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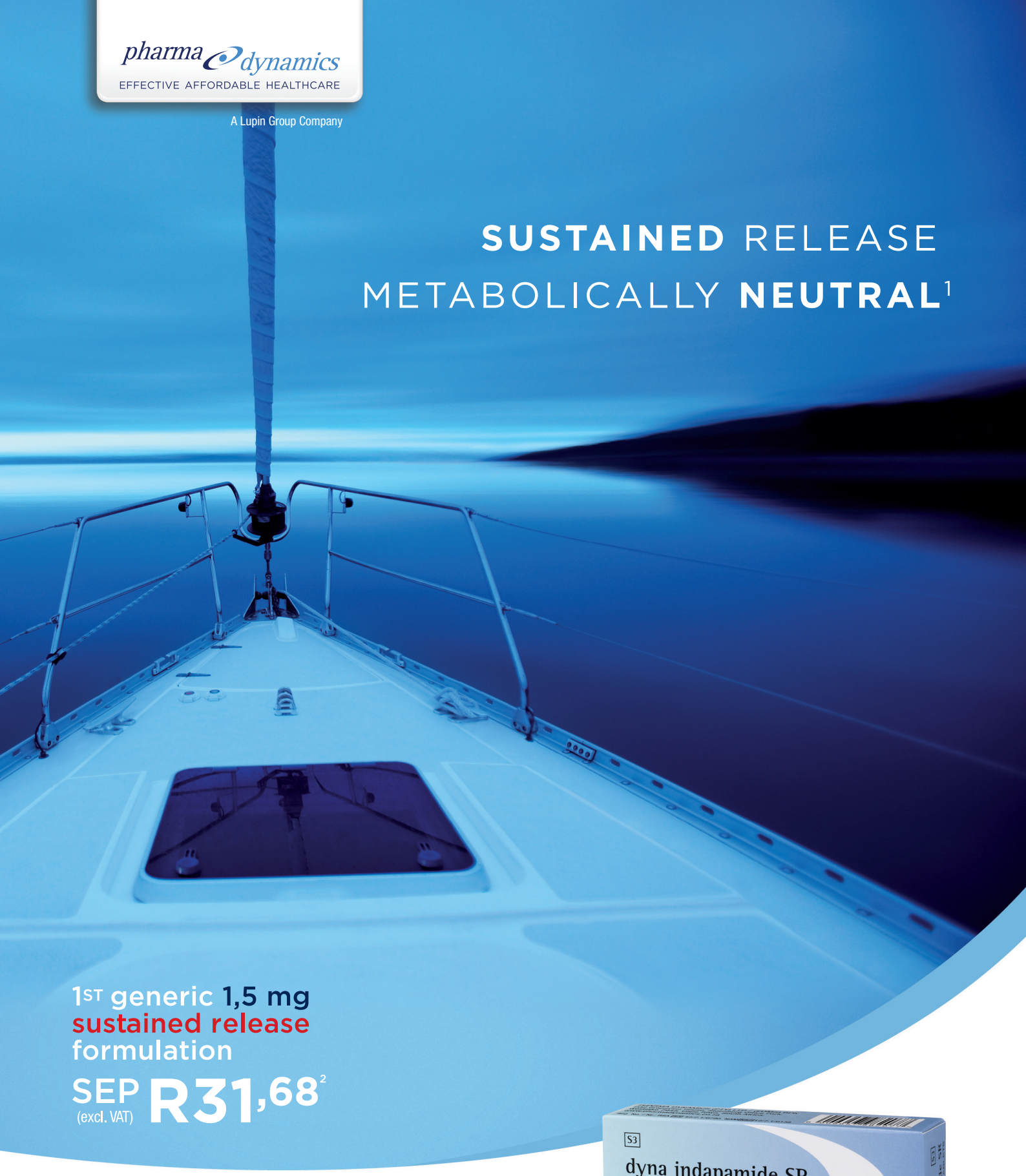

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Editorial

A number of important topics are covered in this issue. The range includes statins, fad diets, telomeres, coronary stents, achievement of cardiovascular risk-reduction targets, and a re-look at the importance of left ventricular hypertension as a risk factor for cardiac disease in diabetes.

Ramsunder, from the University of Stellenbosch, Western Cape, has reviewed the side effects of statins (page 48). This is a frequent query from patients and colleagues, and this article serves as a neat summary that can be provided to them.

In 'Understanding dieting' Naidoo and colleagues from Grey's Hospital, Pietermaritzburg, provide timely comment on fad diets (page 51). They offer a rational approach and insight from a dietitian's viewpoint.

Khan and colleagues provide a fascinating insight into telomere biology and the relevance to atherosclerosis (page 53). This insight opens up a vista of potential new targets for intervention.

Qiao and co-workers from Shandong University, China, provide results from a meta-analysis comparing sirolimus-eluting stents with bare-metal stents. The review showed that sirolimus-eluting stents are safer and more effective than bare-metal stents in coronary artery disease patients with diabetes, in terms of major cardiac events (page 62).

Pinchevsky and colleagues from the University of Witwatersrand, Johannesburg, reviewed the achievement of guideline-recommended targets of major cardiovascular risk factors (page 68). They showed that this is generally sub-optimal, even across different settings. This remains a major clinical problem in patient care around the world.

Lutale and colleagues from Dar es Salaam, Tanzania (page 72), Chillo and co-workers from Dar es Salaam, Tanzania and Bergen, Norway (page 83), and Ajayi and colleagues from Ado Ekiti and Ile Ife, Nigeria, all assessed the importance of the association between left ventricular hypertrophy and hypertension in diabetes. This emphasises the importance of the detection of left ventricular hypertrophy as part of the risk assessment for cardiac disease in diabetes.

The journal staff thank our colleagues from around the world for the important work that they are doing to improve the care of patients with diabetes and we will continue to showcase these efforts.

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Side effects of statins

NIKASH RAMSUNDER

Introduction

The 3-hydroxy 3-methylglutaryl CoA (HMG CoA) reductase inhibitors, also known as statins, were first discovered in 1971 by a Japanese biochemist from the fungus *Penicillium citrinum*. Lovastatin was the first statin introduced on the market in 1987.

Statins are a widely used group of cholesterol-lowering agents that act by inhibiting the enzyme HMG CoA reductase, which catalyses the rate-limiting step in the biosynthesis of cholesterol.[1] They are currently the largest-selling class of pharmaceutical compounds of all time, with six different statins currently available in most parts of the world. With sales in excess of $22 billion per annum, these drugs are taken by hundreds of millions of people around the world to prevent vascular disease.

However these drugs are not without their side effects and it is the purpose of this review to examine some of these side effects. This article will divide these side effects into adverse and beneficial effects.

Adverse effects

By far the most negative side effects of statins are their effects on the muscles, which include myalgia, myositis and rhabdomyolysis, and on the liver, which range from mild asymptomatic transaminitis to severe liver toxicity or damage.[2]

The risk of myositis and rhabdomyolysis was highlighted by the removal of cerivastatin from circulation worldwide in 2001 because of 100 deaths due to rhabdomyolysis. The FDA reported the risk to be at 3.16 per million prescriptions of cerivastatin.[3] However, apart from cerivastatin, serious muscle problems are relatively uncommon with other statins.

Large clinical trials have reported the rate of non-specific muscle or joint aches and pains at around 5%, which was found to be similar in comparator placebo groups.[4] It should be considered, however, that there might be under-reporting of these common muscle aches and pains due to exclusion of patients or their unwillingness to participate in clinical trials by people with known prior intolerance to statins.[2]

Serious muscle problems have been shown to be uncommon in trials conducted thus far, as demonstrated by an analysis of 44 completed trials with 9 416 patients. Only one patient had a creatine kinase level (CK) greater than 10 times the upper limit of normal, 0.4% of patients discontinued the drug due to muscle aches and pains, and none of the patients had rhabdomyolysis.[5]

In another study that included 83 858 patients from several large statin trials where patients were randomly assigned to a statin or placebo, 49 cases of myositis and seven cases of rhabdomyolysis were reported in the statin group compared to 44 and five cases in the placebo group, respectively.[6] The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which was a large, multicentre, randomised, controlled trial, revealed that only one of 5 168 patients treated with a statin had rhabdomyolysis.[7]

The Heart Protection study, where more than 20 000 patients were recruited, showed that more than 33% had muscle complaints such as pain and weakness. Elevated CK levels of more than four times the upper limit of normal were found in only seven of 10 267 patients in the statin-treated patients and one in the placebo group of 10 269 patients.[8,9]

Myopathies can also be divided into toxic myopathies, in which the exact mechanism is unknown, and immune myopathies, which are inflammatory (polymyositis and dermatomyositis) and non-inflammatory (necrotising myopathy without significant inflammation).[10] It must be noted that immune myopathies secondary to statin use are a rare phenomenon.[11]

The exact cause of myopathy remains elusive but seems to be multifactorial. An increased risk of myopathy is associated with factors such as being female, elderly (> 80 years), having a small body frame, with disease of other organ systems, particularly involving the liver and kidney, recent major surgery, excessive physical activity and the consumption of large quantities of grape juice.[12]

The statins also carry a potential risk for adverse liver events, with severe liver disease, cholestatic hepatotoxicity, autoimmune hepatitis, fulminant hepatitis and cirrhosis also a potential problem, but these are exceedingly rare.[2,13,14] Hepatotoxicity is defined as an elevation in aspartate transaminase (AST) and alanine transaminase (ALT) levels to more than three times the upper limit of normal.[15] Large, randomised trials have provided much data regarding the prevalence of liver toxicity and the degree of severity.[8] The Heart Protection Study showed no significant excess in ALT or AST levels, with nine statin patients and four placebo patients having persistent transaminase elevations of more than three times the upper limit of normal.[9]

There were also no significant differences between statin-treated patients and the placebo group in other large-scale trials such as the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial,[16] and the West Of Scotland COronary Prevention Study (WOSCOPS).[17] Acute Liver failure did not occur in any of the above trials and minor elevations in liver enzymes resolved spontaneously with continued treatment.[15] However if an increase in liver enzymes more than three times the upper limit of normal persisted, then discontinuation of therapy was recommended.

The evaluation of a large number of patients has shown that marked elevations in liver enzymes are rare. They potentially occur when other co-morbidities are present, including pre-existing disease, and when the highest dose of statin is used, as well as with drug interactions.[18,19]

Other recorded side effects include cognitive decline, peripheral neuropathy, diabetes, insomnia, tendinitis, arthralgia, arthritis, cataracts and haemorrhagic stroke.[20-22] However these side effects are exceedingly rare.

Beneficial effects

Along with the adverse side effects, there are several beneficial effects that are provided by the statins. These are the cardiovascular

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pleiotropic effects and may be unrelated to the cholesterol-lowering properties of the drug. They include improvement in endothelial dysfunction, normalised vasomotion, increased bioavailability of nitric oxide, anti-oxidant effects, anti-inflammatory effects, plaque stabilization, and inhibition of myocardial hypertrophy.[23]

Treatment with statins has been shown to improve endothelial dysfunction and even improve coronary perfusion in previously ischaemic segments due to improved vaso reactivity.[24] Another small study showed that endothelial function was improved in healthy normocholesterolaemic young males within 24 hours of treatment with atorvastatin.[25] These results show that there is a beneficial effect on endothelial dysfunction, both in the short and long term.

Endothelial dysfunction was also improved by increasing the bioavailability of nitric oxide via prevention of down-regulation of endothelial nitric oxide synthase (eNOS, the enzyme that catalyses the conversion of L-arginine to nitric oxide),[26] and also directly enhancing eNOS activity.

The anti-oxidant effect is another positive side effect of the statins as they have the ability to scavenge free radicals. By reducing the ability of macrophages to oxidise lipoproteins, it is thought that oxidised low-density lipoprotein (LDL) particles become negatively charged and contribute to cytotoxicity and inflammation.

Sanchez-Quesada and co-workers showed this positive effect in patients with familial hypercholesterolaemia who were treated with simvastatin. A reduction of 60% in electronegative LDL cholesterol levels was achieved after six months of treatment.[27] Vaughan and Gotto showed that by reversing the inhibitory effect of LDL cholesterol on eNOS, it caused direct anti-oxidant effects on LDL cholesterol levels.[23]

The anti-inflammatory effects of statins are also well established. The Cholesterol And Recurrent Events (CARE) trial[28] as well as the Pravastatin inflammation/CRP evaluation (PRINCE) trial[29] showed a reduction in levels of high-sensitivity C-reactive protein (hsCRP) in post-myocardial infarct patients. It is this side effect that is one of the reasons for the early beneficial effect in acute coronary syndromes.

Statins have also been shown to have a beneficial effect on the heart musculature as demonstrated in rat models where myocyte hypertrophy was reduced by simvastatin.[30] Another beneficial effect includes the stimulation of endothelial progenitor cell recruitment, whereby endothelial progenitor cells play a role in the repair of ischaemic tissue. Statins have thus been compared to vascular endothelial growth factor (a cytokine that regulates neovascularisation).

Immunomodulation is another area where statins can be of use. It is hypothesised that they inhibit the promoter IV of the major histocompatibility complex-II transactivating factor, which leads to suppression of T-lymphocyte activation.[23]

Conclusion

There is a generous amount of data that has been accrued over more than 25 years to suggest that statins are of great benefit to those with cardiovascular disease. There were initial concerns regarding the adverse effects of statins with regard to myopathy and liver toxicity, but this has been shown not to be clinically relevant. By contrast, there are several promising positive effects of statins on the cardiovascular system that support their greater use. Although statins have displayed a good safety profile, there is still a need for close vigilance and improved reporting of adverse events.

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Letter to the Editor

Dear Sir,

The letter by Mullier[1] in response to our article titled 'The grapefruit: an old wine in a new glass? Metabolic and cardiovascular perspectives'[2] refers. The author states that amiodarone is not only a prodrug but also has inherent pharmacodynamic effects, just like its metabolite N-desethyamiodarone (N-DEA), which he correctly suggests could have even greater pharmacological effects than the parent compound. However, we need to emphasise that even though N-DEA has similar class III anti-arrythmic effects, it has faster sodium channel blockade and lower class IV effects than amiodarone.[3-8]

The inhibition of pre-hepatic/hepatic metabolism of amiodarone by CYP3A4 alters both plasma and cardiac substrate:metabolite ratios. It therefore reduces alterations of PR and QTC intervals,[9] and hence diminishes the anti-arrythmic effects of amiodarone. Both amiodarone and N-DEA have long half-lives (50 and 60 days, respectively),[10-12] and at normal therapeutic doses, the relative contribution of either to the anti-arrythmic and overall cardiac electrophysiological effects is not presently known, despite the aforementioned interaction with grapefruit juice. This, however, does not disqualify amiodarone as a prodrug.

The interaction of grapefruit juice with amiodarone is more complicated than previously thought. Naringenin, the naringin (the predominant flavonoid in grapefruit juice) aglycone, has recently been reported to prolong QTC by inhibiting the rapid component of delayed rectifier K+ current (Ikr), leading to significant QT prolongation in healthy subjects and in patients with dilated or hypertensive cardiomyopathy,[13] as well as in experimental conditions.[14] It is therefore envisaged that the pro-arrythmic actions of naringin or grapefruit juice, just like all class III anti-arrythmic agents, may put patients with myocardial structural disorders at risk of provoking torsades des pointes.

Even though cases of QT prolongation and torsades de pointes with amiodarone are rare, a case has been reported of a female patient who presented with marked QT prolongation associated with ventricular arrhythmias including torsades de pointes, requiring electrical cardioversion after amiodarone administration, after she had been drinking large quantities of grapefruit juice,[15] among others. Perhaps we should have included these references in our previous article to emphasise the fact that the interaction between grapefruit juice and amiodarone is more elaborate than previously thought. We thank the author for pointing out the typing errors in our references.

PMO Owira

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Understanding dieting

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Background

Globally there is a marked increase in the incidence of obesity.[1] As a society, these increasing rates can be attributed to an increased calorie intake, changes in dietary composition, decreasing levels of physical activity, and the active promotion of food consumption by industry.[1]

On a more personal level, factors that contribute to weight gain for the individual include poor dietary intake and food choices, skipping meals, excessive intake of sugar-containing food and drinks, a lack of exercise and inactivity; psychological factors such as depression, anxiety and stress; biomedical factors such as genetic make-up, disorders of metabolism and medical conditions; use of medication; inflammatory processes; and any factors that may result in reduced mobility.[2]

Overweight and obesity are associated with a higher risk of several related conditions, termed chronic diseases of lifestyle, such as chronic kidney disease,[1] cardiovascular disease, diabetes and hypertension. Data show that most deaths that can be attributed to overweight and obesity are due to a cardiovascular event. Even with aggressive drug therapy to target high blood pressure and cholesterol, increased rates of overweight and obesity are expected to have significant negative health effects and increase the prevalence of diabetes, osteoarthritis, certain types of cancer, major vascular diseases,[1] and sleep apnoea.[3] All of these conditions have the potential to lower the quality of life of an individual.

Weight loss of only five to 10% in obese individuals significantly reduces the above risks.[4] Sustained weight loss of as little as three to 5% is likely to result in clinically significant reductions in triglyceride and blood glucose levels, and the risk of developing type 2 diabetes, and better long-term control of blood glucose levels.[5]

Goals

Our goal as a society is to reduce the prevalence of obesity and associated risks. For the individual living with excess weight every day, a self-imposed goal tends to be more personal and urgent, with the intention of simply losing as much weight as necessary to be comfortable and confident, as quickly as possible.

There are diets that promise rapid weight loss, with minimal effort, but is it realistic to expect this when weight gain has been gradual? And if it is this simple, why does the topic spark such controversy?

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Fad diets

A fad diet is the term used to describe diets that gain popularity and then quickly diminish in importance. The loss of interest may be the result of the difficulty maintaining the extreme measures used to encourage weight loss in some of these diets.

Some common characteristics of fad diets are the rigid menus and monotonous food choices, unlimited foods of some type, a lack of scientific evidence to support the claims, the introduction of 'magical' foods, food combinations or newly discovered secrets, and the use of scientific jargon and incomplete information or half-truths. These diets may also involve the purchase of a commercial product,[6] intermittent fasting,[7] cutting out or excessively restricting certain food groups, and excessively promoting the value of another. Some examples are low-carbohydrate diets, which are high in fat and high or low in protein; the blood group diet; the alkaline diet; and one-food diets, such as the cabbage soup and grapefruit diets.

Fad diets sometimes do not acknowledge the importance of physical activity as part of a weight-loss plan,[6] disregarding one of the most important components of a healthy lifestyle. Appropriate weight loss requires a combination of diet, exercise and behavioural modification.[8]

Fad diets can also present the dieter with little variety, which makes it difficult to sustain, and necessitates a lot of planning. The lack of balance of nutrients can mean supplementation is necessary, which can be expensive to maintain.[9]

Some fad diets are sometimes simply a low-kilojoule diet by a different name, and therefore can result in weight loss.[6] Low-carbohydrate diets can result in initial rapid weight loss, as they are also low-kilojoule diets. However, energy–protein balance studies have shown that the greater weight loss on a low-carbohydrate, high-fat diet is accounted for by losses in water.[10] The aim of weight loss diets should be the loss of weight from fat. Water and muscle loss, among the other consequences of fad diets, can be detrimental to one's health.

Significant consequences of fad diets

Rapid weight loss, greater than 500 g to 1 kg per week, represents loss from lean muscle mass and fluid.[2] Weight regained thereafter is usually fat rather than muscle, and this yo-yo dieting effect has adverse effects on the heart and can even lead to cardiac injury and death.[2]

High-protein diets can place great strain on the kidneys, due to the greater production of waste products of protein breakdown,

and in the long term have the potential to increase the risk of osteoporosis due to increased calcium excretion via the same pathway.[6]

On a low-carbohydrate diet, once carbohydrate stores have been used up, the only source of glucose available to the body is from allowing the body to produce glucose using muscle and liver stores.[2] Some tissues in the body, such as the brain and red blood cells, have an obligate requirement for glucose as their energy source.[2,6] Elimination or excessive reduction of carbohydrates in the diet results in a reduction in fibre and whole-grain food intake, which commonly leads to constipation. Persistent constipation over the long term may lead to diverticular disease, which can increase the risk for colon cancer.[2]

Restrictive diets have been found to result in vitamin, mineral and protein deficiencies, cardiac, renal and metabolic disorders, and even death. Very low-calorie diets will not sustain life for long.[11] If only a very small amount of lean meat, fish and low-fat dairy is allowed, there is the risk of inadequate intakes of calcium, iron, zinc and high-quality protein.[6] The cabbage soup or grapefruit diets, which emphasise one food and exclude all others, is nutritionally unbalanced and unscientific,[6] and can also lead to nutritional deficiencies. The claims made by proponents of some fad diets and health foods, of superior health and freedom from disease, can result in delays in people seeking necessary and competent medical attention,[12-15] which can exacerbate this problem.[16]

Food and mealtimes should not be a source of anxiety; it should be part of the pleasure we derive from social interaction, and not a reason to avoid it. Food faddism can promote inappropriate behaviour around food. It is important to examine what behaviour the eating plan elicits; you should not accept feeling intense frustration when food-related practices are disrupted, guilt or self-loathing when food transgressions are committed, chronic worry about non-optimal health or food imperfection or intrusive thoughts about food at inappropriate times.[17] Balanced eating should negate the need to behave obsessively around food.

Balanced diets

A balanced diet for overall health recommends an intake of 45 to 60% energy from carbohydrates, approximately 30% from fat, depending on the medical history of the individual, and the remaining energy from protein, however exceeding 15 to 20% energy from protein is not always safe.[2] A balanced diet should include food from all food groups, in appropriate amounts.

A realistic, balanced diet should not require the purchase of any commercial product and it can be sustained in the long term. Balanced eating is safe for the whole family and results in less isolation and less time spent on planning menus appropriate for different family members. Best of all, it aids in the prevention of diseases by helping to reduce risk factors and meet nutrient requirements.

Questions to ponder when choosing a diet

- Is the information provided by a medical professional who is accountable to a governing body? If so, is he/she willing to take responsibility for the advice given, and is he/she available for follow-up advice and questions?[6]
- Does the diet promote gradual, sustainable weight loss of 0.5 to 1 kg per week,[6] and not more than five to 10% of body weight in six months?
- Does the diet include food from all food groups in adequate amounts, such as fruit and vegetables, cereal foods, low-fat dairy and lean meats?[6]
- Is there overemphasis on any one food type?[6]
- Does the diet recommend increased levels of physical activity?[6]
- Can you eat this way for the rest of your life?[18] Is it easy to maintain and does it promote long-term health?
- What are the financial implications of being on this diet? Is it realistic and are foods readily available?

Conclusion

Any weight-loss plan undertaken should ultimately promote health and well-being. It is important to remember that any clinical condition requires the assistance of a medical professional to diagnose and discuss treatment options with you, as an informed patient. Your health is your responsibility and within your control.

Although a panacea for all weight woes would make weight loss simpler, it is not advisable to aim for rapid weight loss on a diet that negates the body's need for balance. Food, delicious and varied, is necessary to supply all the body's nutrient requirements.

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Telomeres and atherosclerosis

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Abstract

In humans and other multicellular organisms that have an extended lifespan, the leading causes of death are atherosclerotic cardiovascular disease and cancer. Experimental and clinical evidence indicates that these age-related disorders are linked through dysregulation of telomere homeostasis. Telomeres are DNA protein structures located at the terminal end of chromosomes and shorten with each cycle of cell replication, thereby reflecting the biological age of an organism. Critically shortened telomeres provoke cellular senescence and apoptosis, impairing the function and viability of a cell. The endothelial cells within atherosclerotic plaques have been shown to display features of cellular senescence. Studies have consistently demonstrated an association between shortened telomere length and coronary artery disease (CAD).

Several of the CAD risk factors and particularly type 2 diabetes are linked to telomere shortening and cellular senescence. Our interest in telomere biology was prompted by the high incidence of premature CAD and diabetes in a subset of our population, and the hypothesis that these conditions are premature-ageing syndromes. The assessment of telomere length may serve as a better predictor of cardiovascular risk and mortality than currently available risk markers, and anti-senescence therapy targeting the telomere complex is emerging as a new strategy in the treatment of atherosclerosis. We review the evidence linking telomere biology to atherosclerosis and discuss methods to preserve telomere length.

Keywords: coronary artery disease, molecular and cellular cardiology

Atherosclerosis is an age-related disorder.[1] Premature biological ageing, an entity separate from chronological ageing, may contribute to its pathogenesis. Cellular senescence, which is defined as the finite replicative lifespan of cells leading to irreversible growth arrest, plays a critical role in the pathogenesis of atherosclerosis.[2-4]

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A central feature of atherosclerosis is vascular endothelial cell dysfunction.

The histology of atherosclerotic plaques has been comprehensively studied and has demonstrated that endothelial and vascular smooth muscle cells in atherosclerotic lesions display changes of senescence.[5,6] In stable atherosclerotic plaques there are few senescent cells, whereas in advanced, complicated plaques, senescent cells accumulate because of high cell turnover and increase the risk of acute coronary syndromes.[7]

The biological mechanism that triggers the onset of cellular senescence is thought to be telomere shortening. Telomeres are DNA protein structures located at the extreme ends of the chromosomes.They cap and protect the ends of chromosomes. Whereas the DNA molecule carries the genetic code and is about 100 million base pairs long, the telomeric ends are non-coding and are between 5 000 and 15 000 base pairs long: 15 000 at the time of human conception and around 5 000 at the time of death.[8]

During DNA replication, the very end sequences of the telomere are not fully copied due to the inability of DNA polymerase to completely replicate the chromosome to its very end. This is termed the end-replication problem. As a result, between 50 and 200 nucleotides are lost with each cycle of cell replication, leading to progressive telomere shortening.[9] When telomere length reaches a critical threshold, the cell becomes incapable of further replication and enters a phase of cellular growth arrest termed replicative senescence. On average, cells reach senescence after 50 divisions. The senescent phase may then progress to cell death or apoptosis.

Cellular senescence and the apoptotic cascade are mediated by cell cycle checkpoint pathways, regulated mainly by p53/p21, which are best recognised as tumour suppressor proteins.[2] This process is responsible for physiological ageing and gives rise to the morphological and functional changes that accompany the decline in organ function seen with age, e.g. endothelial cell senescence in atherosclerotic plaques or beta-cell senescence in diabetes mellitus.[4,10,11]

However, a limited number of cells (about one in 10 million) are able to reactivate the enzyme telomerase. In the presence of telomerase, cells are able to replicate and in this way telomere integrity is maintained. Telomerase activity is lacking in somatic cells but is preserved in reproductive and stem cells. High telomerase activity has also been detected in about 90% of human cancer samples. The high telomerase activity is thought to be responsible for the indefinite cell proliferation and cellular immortalisation seen with cancer.[12-15] Inducing cell senescence and apoptosis is therefore an important mechanism for the suppression of cancer.

Studies have shown that telomere length is not only determined by cell replication and lifespan, but is also influenced by heredity and exposure to environmental risk factors. The healthy offspring of parents with coronary artery disease have shorter telomeres than the offspring of normal subjects.[16,17] The traditional risk factors for atherosclerosis have been shown to lower the threshold for cardiovascular disease by hastening biological aging.[18] Risk factors such as smoking,[19,20] obesity,[19] insulin resistance,[21,22] and type 2 diabetes[23-26] are associated with accelerated telomere shortening.

Diabetic patients, more than any other subset, show the greatest difference in telomere length compared to non-diabetics.[26] Type 2 diabetes is considered a cardiovascular risk equivalent.[27,28] It is postulated that telomere shortening induces pancreatic β-cell senescence. Like atherosclerosis, diabetes is thought to be a premature-ageing syndrome.[26]

The study of telomeres may therefore provide in a single marker, the combined influence of genetics, environmental risk and ageing in predicting risk and identifying susceptible individuals prone to developing coronary artery disease. This is especially relevant in our community, which has a high incidence of both premature coronary artery disease and type 2 diabetes.[29,30]

Structure and function of the telomere complex

Telomeres have a dynamic structure that is thought to switch between a closed, protected state and an open, extendable state, which allows the DNA terminus to undergo replication. The protected state is necessary for safeguarding the integrity of genomic material, whereas the extendable state allows the enzyme telomerase to extend short telomeres (Figs 1, 2).[31]

Telomere components include:

- The DNA component: this consists of tandem repeats of the hexanucleotide 5′-TTAGGG-3′ (T = thymine, A = adenine, G = guanine) and has a high guanine content. The bulk of telomeric DNA is arranged in the double-stranded configuration, which then ends in a single-stranded extension. The single-stranded overhang folds back to form a terminal loop, which prevents the end of the telomere from being recognised as a damaged, broken end. Telomere shortening is thought to destabilise this loop.[8,14,31]
- Shelterin proteins: these proteins bind and protect the loop structure and are termed shelterin because they shelter the chromosome end.[32] An inability to form the terminal loop will leave the chromosome ends uncapped, resembling a DNA break and provoking DNA repair mechanisms. The shelterin complex consists of six proteins, which have specific functions in telomere replication and end protection.

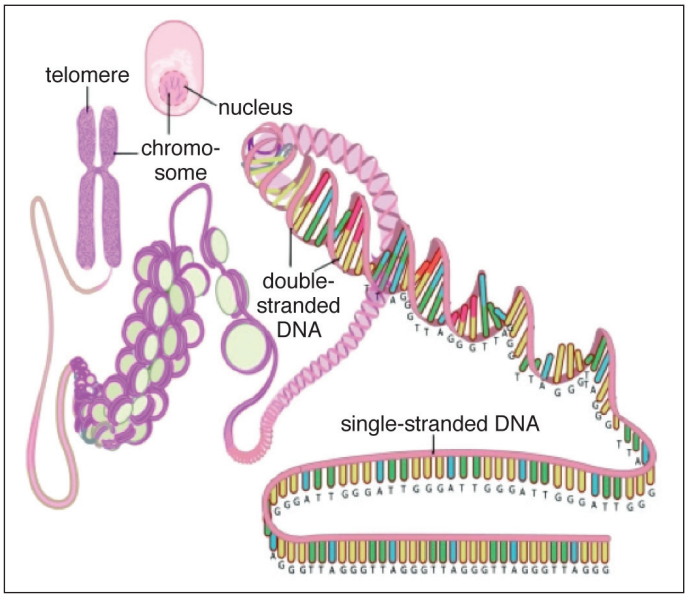

Figure 1. A simplified scheme depicting the structure of the telomere and its location on the chromosome in the cell. Reproduced with permission.[126]

The six proteins are: TRF1 and TRF2: telomere repeat binding factors 1 and 2, which are the two major proteins; POT1: protection of telomeres 1; TPP1: tripeptidyl peptidase 1; TIN2: TRF1-interacting protein 2; and RAP1: repressor activator protein 1. Whereas the shelterin proteins are a constant fixture at the telomere end, other accessory proteins are intermittently recruited to the telomere. These proteins include the tankyrases tank 1 and 2, Ku 70/86 and poly-ADP ribose polymerase-1 (PARP-1), which influence the control of telomere length and repress the DNA damage response.[31,33,34]

- The CST complex: an additional telomere-associated complex, known as the CST, has recently been identified. It binds single-stranded DNA and appears important for both telomere protection and replication.[31]
- Telomerase: in order for cellular repair to take place as well as for species survival, stem cells and reproductive cells need to be able to proliferate without the penalty of progressive telomere shortening.[31] These cells, unlike somatic cells, contain the enzyme telomerase, which is capable of adding DNA sequences to the chromosome terminus to compensate for the loss sustained during replication. Telomerase is made of Terc – the RNA component that serves as a template for the synthesis of new telomeric DNA, and TERT – a reverse transcriptase which is the catalytic subunit representing the rate-limiting step in telomerase activity.[12,14,33,35] A variety of accessory proteins have important roles in telomerase biogenesis and localisation.

Telomere homeostasis

Telomere length in proliferating cells is influenced by the following factors.

- Factors that shorten telomeres:
  - telomere attrition during cell division
  - DNA damage due to oxidative stress caused by environmental risk factors
  - specific exonucleases involved in the degradation of RNA primers used for DNA replication
  - deficiency of Rad 54, which is involved in DNA repair
  - histones: methylation of histones H3 and H4 diminishes telomerase activity.[36]
- Factors that maintain telomere length:
  - Telomerase: in addition to the level of telomerase within a cell, telomere length is also dependent on the delivery of

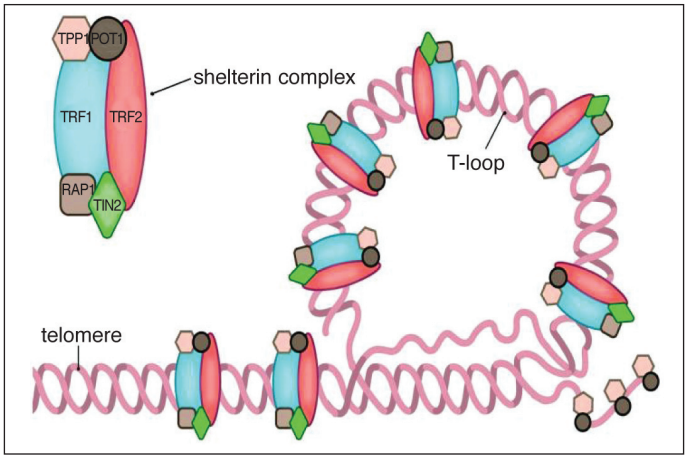

Figure 2. Scheme showing the terminal end of the telomere concealing the terminal single-stranded part with the help of the shelterin complex. Reproduced with permission.[126]

telomerase to the telomere by Cajal bodies, telomerase access to the DNA terminus and the presence of molecules that stimulate or inhibit telomerase activity.[31]

– A recombination process known as alternative lengthening of telomeres or ALT (10% of cancers maintain their telomere length by ALT).[35,37]

The two major mechanisms responsible for telomere shortening are the end-replication problem, and more importantly, the oxidative DNA damage induced by environmental risk factors. Telomere shortening due to the end-replication problem is relatively small and constant in each cell, irrespective of telomere length, whereas telomere shortening induced by oxidative stress is proportional to telomere length, as longer telomeres are larger targets for free radicals.[38-40]

Variability in telomere length is also noted at birth and is influenced by heredity, race and gender. Telomere length has been shown to be shorter in healthy offspring of patients with coronary artery disease (CAD).[16,17] This finding offers some explanation for the increased familial risk of CAD and also implies that shorter telomeres are likely a primary abnormality in the pathogenesis of the disease.[41] African-Americans have longer telomeres than whites and Indians,[42-44] and females have longer telomeres than their male counterparts.[45]

Mechanisms of disease: a balance between injury and repair

Mechanism of injury: oxidative stress

Oxidative stress is the unifying pathophysiological mechanism responsible for ageing and age-related disorders.[46-49] It is defined as an increase in the intra-cellular concentration of reactive oxygen species (ROS). ROS are generated during regular metabolism because of incomplete oxygen reduction in the mitochondrial electron transport chain – a one-electron reduction of oxygen forms superoxide (O_2^-), a two-electron reduction forms hydrogen peroxide (H_2O_2), and a three-electron reduction forms the hydroxyl radical (OH). Many other ROS species can be derived from superoxide and hydrogen peroxide.

These ROS initiate processes involved in atherogenesis through several enzyme systems including xanthine oxidase, NADPH (nicotinamide adenine dinucleotide phosphate) oxidases and nitric oxide synthase.[50] The ROS damage all components of the cell including proteins, lipids and DNA. The exact mechanism of damage is via:

- Decreased availability of nitric oxide (NO), which results in defective endothelial vasodilation. Nitric oxide is an antiatherosclerotic agent that protects vascular cells from apoptosis.[51-53]
- Inflammation: ROS increase the production of pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), which in turn can also increase the production of ROS. TNF-α activates two transcription factors: nuclear factor kappa-β (NF-κβ) and activator protein-1 (AP-1), which increase the expression of pro-inflammatory genes. Cytokines stimulate the synthesis of acute-phase reactants such as C-reactive protein (CRP) by the liver. ROS also increase the expression of cellular adhesion molecules on the endothelial cell surface. These molecules, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), enhance monocyte adhesion to endothelial cells and lead to the formation of atherosclerotic plaques.[54-58]
- Modification of lipoproteins and lipids: ROS contribute to the formation of lipid peroxides, which bind to proteins to form advanced lipoxidation end products (ALEs).[59] Oxidised LDL and ALE-containing LDL are pro-atherogenic. *In vitro* studies have shown that LDL cholesterol (LDL-C) is not atherogenic in itself but it is the oxidative modification of LDL-C that plays a critical role in the pathogenesis of atherosclerosis.[60,61] In the early phase of atherosclerosis, oxidised-LDL (ox-LDL) contributes to inflammation by enhancing expression of chemokines such as the monocyte chemo-attractant protein-1. Ox-LDL decreases the bioavailability of nitric oxide. The proatherogenic effects are exerted by influencing the phosphoinositol-3 (PI3) kinase/Akt signalling pathway.[62]

This pathway has an important regulatory role in cellular proliferation and survival. Of the three known isoforms of Akt, Akt 1 is most relevant in regulating cardiovascular cell growth and survival and Akt 2, which is highly expressed in muscle and adipocytes, contributes to regulation of glucose homeostasis. These isoforms are activated by growth factors, extra-cellular stimuli such as pro-atherogenic factors and by oncogenic mutations in upstream regulatory proteins. Akt mediates downstream signalling pathways through phosphorylation of a host of substrates. Thus far, more than a hundred substrates for Akt have been identified, indicating that it has widespread biological effects. Dysregulation of Akt is associated with cardiovascular disease, diabetes, cancer and neurological disorders.

Our current understanding of its role in cardiovascular disease is incomplete and studies explaining its effects describe conflicting mechanisms. Breitschopf *et al*. have demonstrated that pro-atherogenic factors such as ox-LDL, TNF-α and hydrogen peroxide promoted endothelial cell senescence by inactivation of the PI3/Akt pathway. Akt was shown to maintain telomerase activity by phosphorylation of its TERT subunit, and inactivating Akt reduced telomerase activity, leading to accelerated endothelial cell senescence.[63]

On the other hand, Miyauchi *et al*. demonstrated that activation of Akt promotes senescence and arrests cell growth via the p53/p21-dependent pathway and that inhibition of Akt extends the lifespan of primary cultured human endothelial cells. Akt achieved growth arrest by phosphorylating and inhibiting a forkhead transcription factor (FOXO 3a), which influences p53 activity by regulating levels of ROS.[64] Rosso *et al*. confirmed the latter mechanism by demonstrating that endothelial progenitor cells cultured in the presence of ox-LDL in a diabetic milieu underwent senescence and growth arrest by activation of the Akt pathway via accumulation of p53/p21.[65] Miyauchi *et al*. commented that the divergent observations may be explained by the different cell types used in studies. They used primary human endothelial cells, whereas most other studies examined immortal cells in which the normal cell cycle machinery may have been impaired. In addition, Akt may promote cell proliferation or senescence depending on other factors such as the duration and extent of its activation. It has been noted that activation of Akt in itself is insufficient to cause cancer unless combined with other oncogenic stimuli.

There is currently much interest in the development of Akt inhibitors for the treatment of cancer and it remains to be seen what effects such therapy would have on the cardiovascular system. In addition to Akt signalling, mitogenic stimuli

may activate Ras signalling, which has also been shown to participate in the divergent processes of both cell proliferation and senescence.[66]

Oxidative stress and telomere shortening

Exposure of DNA to oxidative stress produces higher levels of stress biomarkers in telomere sequences than in non-telomere sequences. 8-oxodG (8-oxo-7,8-dihydro-2-deoxyguanosine) is a sensitive biomarker for oxidative stress on DNA. Progressive increases in 8-oxodG have been shown to correlate with decreasing telomere length. The high guanine (-GGG) content of telomeres makes them particularly sensitive to damage by oxidative stress.[47,67]

This site specificity for guanine is due to several reasons. Firstly, guanine is the most easily oxidised DNA base as its oxidation potential is lower than that of the other three bases (adenine < cytosine < thymine). A second factor is the distribution of electrons on the DNA base. The highest occupied molecular orbital that accommodates electrons with the greatest energy determines the reactivity of DNA bases. Many of these electrons are located on the 5′-G of the GG sequence and therefore this guanine is more likely to be oxidised.

A third reason is that the ROS have different redox potentials, which may determine site specificity. For example, the free hydroxyl radicals cause DNA damage without a marked site specificity, whereas the benzoyloxyl radicals specifically cause damage to the 5′-G in GG sequence.[68-70] In addition to the direct effects of ROS, telomeres, unlike the rest of the genome, appear less efficient in repairing oxidative damage.[71] An important consequence of oxidative stress is the initiation of an inflammatory response.

Inflammation and telomere shortening

Chronic systemic inflammation is responsible for an increase in peripheral white blood cell turnover, which in turn leads to an exaggerated telomere attrition rate.[55] The increased white cell consumption induces haematopoietic stem cells to divide, thereby shortening their telomere length as well. Exposure to TNF-α also reduces telomere length by negative regulation of telomerase activity.[57]

DNA sampling for telomere length quantification is generally sourced from circulating white blood cells rather than human vascular tissue. It has been suggested that white blood cell telomere attrition is a consequence of systemic inflammation rather than being indicative of vascular endothelial cell ageing. The study by Wilson *et al*. demonstrated that telomere attrition in circulating blood leucocytes reflects similar changes in the vasculature and is an acceptable surrogate for vascular ageing in population studies.[72]

Mechanisms of repair: stem cells and endothelial progenitor cells

The atherosclerotic process is characterised by endothelial cell dysfunction. Repair of the endothelium is dependent on the presence of endothelial progenitor cells, which migrate to sites of vascular injury to initiate repair. Endothelial progenitor cells are produced by haematopoietic stem cells, which, due to their higher telomerase activity, have a greater proliferative capacity. Exhaustion of the progenitor cell or stem cell pool is an important factor in endothelial cell dysfunction. Telomere length in haematopoietic stem cells (HSC) is a reflection of progenitor cell reserves, and shortened telomere length in these cells is indicative of diminished reparative capacity.[41,42]

The onset of atherosclerotic disease is therefore dependent on the balance between injury and repair of the endothelium – injury from oxidative stress and inflammation, and repair, which depends on haematopoietic stem cell reserves, as reflected by HSC telomere length.[41]

Telomeres and atherosclerosis risk factors

Smoking

Cigarette smoking is associated with increased oxidative stress.[73] Although there is variability in the findings of different epidemiological studies, the following studies recorded an association between smoking and telomere shortening. Nawrot *et al*., reporting on the Flemish study on environment, genes and health outcomes, found shorter telomeres in smokers compared to non-smokers.[45] The study by Valdes *et al*. showed that women who had never smoked had longer telomeres than former smokers, and both had longer telomeres than current smokers (531 never smokers, 369 ex-smokers and 203 current smokers).

They also demonstrated a dose-dependent relationship between smoking and telomere shortening. Each pack-year smoked was equivalent to the loss of an additional five base pairs of telomere length, or 18% of the average annual loss in telomere length, compared to the rate in the overall cohort.[19] The dose-effect relationship was subsequently replicated by Morla *et al*. who studied a cohort of male smokers with and without chronic obstructive pulmonary disease (50 smokers, 26 never smokers) in whom telomere shortening correlated with cumulative exposure to tobacco smoking.[20]

Hypertension

Since systolic blood pressure rises with age, and diastolic blood pressure plateaus, Jeanclos *et al*. postulated that arterial pulse pressure may correlate with biological age. Among 49 twin pairs (mean age 37 years) in the Danish Twin Register, they showed a significant inverse correlation between pulse pressure and telomere length, i.e. wider pulse pressure was associated with shorter telomere length.[74]

The Framingham Heart Study found shorter telomere lengths in hypertensive males (n = 171) compared to their normotensive peers (n = 156) but the shorter telomere length was largely due to insulin resistance.[21] Benetos *et al*. examined the relationship between telomere length and carotid artery atherosclerosis in 163 treated hypertensive males and found that telomere length was shorter in hypertensive men with carotid plaques compared to hypertensive men without plaques.[75]

Obesity

Increased caloric intake and obesity are recognised to shorten lifespan. Adipose tissue is not only a source of ROS and pro inflammatory cytokines but also secretes a host of bioactive molecules including angiotensinogen, leptin, resistin, adiponectin and PAI-1, which influence the function and structural integrity of the cardiovascular system.[76,77] These adipocytokines influence glucose metabolism, blood pressure regulation, lipid metabolism, the coagulation system and endothelial function to accelerate the process of atherosclerosis.

Obesity is strongly associated with cardiovascular disease and promotes the clustering of risk factors such as dyslipidaemia, hypertension, diabetes and the metabolic syndrome. Obese individuals experience substantially elevated morbidity and mortality from all forms of cardiovascular disease.[78,79]

A retrospective analysis of the Bogalusa Heart Study examined the relationship between weight change and telomere dynamics over a period of 10 to 12 years in 70 young adults. The study showed that weight gain was associated with accelerated telomere attrition and that a rise in insulin resistance accounted for the relationship between the increase in body mass index (BMI) and telomere attrition rate.[22]

In the study by Valdes *et al*. of 1 122 healthy adult female twins (45 monozygotic and 516 dizygotic pairs, mean age 47 years), it was found that the telomeres of obese twins were 240 base pairs shorter than those of the lean sibling. The difference in telomere length between the lean and the obese corresponded to 8.8 years of ageing.[19] The study also suggested that the mechanism by which obesity affects telomere length is through increased leptin levels rather than BMI *per se*.

Obesity is associated with high serum concentrations of leptin, which is linked to NF-κB activation, a mediating factor in the production of ROS and inflammatory cytokines.[80] Nordfjall *et al*. confirmed the negative association between BMI and telomere length but in their study, this finding applied only to female participants.[81]

Insulin resistance

Insulin resistance is pro-atherogenic and increases the risk of CAD even without the presence of hyperglycaemia.[82] The mechanisms involved in atherogenesis include both systemic effects such as dyslipidaemia, hypertension and a pro-inflammatory state as well as direct effects on vascular endothelial cells, smooth muscle cells and macrophages. These three cell types have insulin receptors and effects are mediated via down-regulation of insulin signalling pathways such as the Akt pathway.

In early atherosclerosis, insulin resistance causes decreased nitric oxide production and an increase in VCAM-1, which are responsible for impaired vasodilation and inflammation. In advanced plaques, insulin resistance triggers apoptosis of cells via the Akt pathway.[83-86] Apoptosis of smooth muscle cells causes fibrous cap thinning, whereas apoptosis of macrophages leads to plaque necrosis, both being pathological processes that precipitate acute coronary syndromes.

Diabetes

In the setting of type 2 diabetes, insulin resistance and hyperglycaemia have additive effects that accelerate the process of atherosclerosis. Hyperglycaemia is associated with the activation of several molecular pathways that include the production of advanced glycation end products (AGEs),[87,88] activation of protein kinase C, increased activity of both the polyol as well as the hexosamine pathways.[89,90] These pathways are interdependent and induce cellular damage through the final common mechanism of increased oxidative stress.

It is well established that hyperglycaemia, even in the pre-diabetic state, induces oxidative stress[91-94] and ultimately leads to cellular senescence. Cellular senescence and apoptosis occur not only in vascular endothelial and smooth muscle cells but in multiple cell lines, including endothelial progenitor cells.[95,96] Type 2 diabetes can therefore be considered a premature-ageing syndrome.

In recent years several cross-sectional clinical studies have been published that demonstrate an association between shorter telomere length and type 2 diabetes (T2D).[23-26,97-99] The studies suggest that there is a gradation in the severity of telomere shortening. Shorter telomere lengths were noted in patients with impaired glucose tolerance compared to controls, even shorter lengths in those with diabetes, and the shortest lengths were observed in patients with the combination of pre-diabetes/diabetes and atherosclerotic vascular disease, compared to those with diabetes or cardiovascular disease alone.[100]

Satoh *et al*. showed that CAD patients with the metabolic syndrome had shorter telomeres than CAD patients without the metabolic syndrome.[97] Adaikalakoteswari *et al*. found that among diabetic patients, those with atherosclerotic plaques had shorter telomeres.[98] The study by Olivieri *et al*. demonstrated that diabetic patients with myocardial infarction had shorter telomeres than diabetic subjects without myocardial infarction,[99] and the study by Salpea *et al*. showed that among diabetic subjects, those with CAD had significantly shorter telomeres.[26]

Based on these observations, it has been postulated that critically shortened telomeres, due to a combination of inherited short telomeres and oxidative stress-induced telomere attrition, caused by the common risk factors between diabetes and cardiovascular disease, indicates greater cellular ageing in vascular endothelial cells and pancreatic beta-cells, and may be a useful biomarker of tissue ageing and disease progression.[100]

Atherosclerosis and coronary artery disease

Minamino *et al*. have shown that endothelial cells with characteristic features of senescence are present in atherosclerotic regions of human coronary arteries. They demonstrated that inhibiting telomere function induced senescence in endothelial cells, whereas introducing telomerase suppressed senescence and extended the lifespan of these cells.[3]

Ogami *et al*. have shown that the telomeres of coronary endothelial cells were shorter in patients with CAD compared to age-matched subjects without CAD and that in the CAD patients, telomere length was shorter in endothelial cells at atherosclerotic sites compared to non-atherosclerotic sites.[101] Chang and Harley have shown that endothelial cells in regions of the vascular tree that are subjected to greater haemodynamic stress demonstrated more pronounced telomere attrition than endothelial cells from areas with less shear stress. For example, telomere attrition rate in the iliac arteries was –147 base pairs per year compared to the internal mammary arteries at –87 base pairs per year.[102]

Okuda *et al*. also demonstrated that telomere attrition was higher in the intima of the distal abdominal aorta compared to the proximal abdominal aorta, again indicating that areas of the vasculature that undergo greater shear wall stress have higher cellular turnover rates and consequently shorter telomere length.103 This variable telomere attrition rate indicates the significant impact of environmental stress on telomere length.

Population studies have demonstrated a link between telomere length and CAD.[104,105] In the pioneering study by Samani *et al*. of 10 cases and 20 control subjects, it was observed that mean telomere length was significantly shorter in patients with severe triple-vessel CAD compared with matched subjects who had normal coronary angiograms.[106]

A retrospective registry analysis of 383 patients (203 cases, 180 controls) showed that patients with premature myocardial infarction had significantly shorter mean telomere lengths. In this study the difference in telomere length between cases and chronologically age-matched controls demonstrated a biological age gap in excess of 11 years. Compared with subjects in the highest quartile for

telomere length, the risk of myocardial infarction was increased between 2.8- and 3.2-fold in subjects with shorter-than-average telomeres.[107] In another study of 143 normal blood donors over the age of 60 years, it was shown that subjects with shorter telomeres had poorer survival, with a 3.18-fold higher mortality rate from heart disease.[108]

In a sub-study of the West of Scotland Primary Prevention Study (WOSCOPS) that compared telomere lengths at recruitment in 484 individuals who went on to develop coronary heart disease events with those from 1 058 age-matched controls who remained free of CAD, it was shown that subjects with shorter telomere length at the time of recruitment had a significantly higher risk of developing subsequent coronary heart disease.[109] In a case-control sub-study of the Cardiovascular

Health Study that examined 419 older subjects, it was found that individuals 73 years or younger had a threefold increased risk of myocardial infarction and stroke for each one kilobase decrease in telomere length.[110]

Farzaneh-Far *et al*. measured telomere length in 780 patients with stable angina in a prospective cohort study. During a mean follow up of 4.4 years, shorter telomere length was significantly associated with all-cause mortality, independent of age, clinical and echocardiographic variables.[111] Zee *et al*. using samples collected at baseline in the prospective Physician's Health Study from a cohort of 14 916 initially healthy men, of whom 337 went on to develop myocardial infarction, demonstrated that participants with shorter telomere length at baseline had a significantly increased risk of incident myocardial infarction compared to age- and smoking-matched controls who remained free of vascular disease over a mean follow up of 3.85 years.[112]

Finally, in the prospective population-based Bruneck study, baseline telomere length was a significant risk predictor for subsequent myocardial infarction and stroke, independent of standard risk factors. Of note in this study was that telomere length was strongly associated with advanced pathology and acute vascular syndromes but not early atherosclerosis.[7]

Mechanisms to preserve telomere length

Telomerase has been shown to be activated by lifestyle choices that include a healthy diet, stress relief through meditation, chronic high-intensity aerobic physical exercise as well as by pharmacological agents.[113,114]

Exercise has been associated with improved cardiovascular health and longevity. La Rocca *et al*. in a recent study have shown that maintaining high levels of aerobic fitness preserved telomere length.[115] They examined young and old individuals and compared sedentary subjects who exercised fewer than two days per week for less than 30 min per day with active ones who had exercised five days per week for more than 45 min per day for five years. Telomere length was preserved in the older adults who performed chronic, vigorous exercise and was positively correlated with maximum aerobic capacity as assessed by higher $VO2_{max}$ levels.

The molecular mechanisms exploring the protective effects of exercise on the heart has been studied in experimental animals. Exercise has been shown to promote cell survival by increasing the activity of telomerase and the expression of TRF2. The up-regulation of telomerase was mediated via insulin-like growth factor 2 and endothelial nitric oxide synthase. Exercise was also shown to decrease levels of markers of cellular growth arrest and apoptosis, such as p16, cell cycle-checkpoint kinase 2 and p53.

Molecules that enhance low residual telomerase activity or re-express silenced telomerase may help preserve telomere length. Natural products such as derivatives from the Chinese Astragalus plant, *Ginko biloba* and resveratrol have been shown to activate telomerase, the latter two via PI3k/Akt signalling pathways. The anti-oxidants N-acetylcysteine and α-tocopherol enhance telomerase activity.[116,117] Farzaneh-Far *et al*. demonstrated in a prospective study of patients with stable CAD, an inverse relationship between baseline blood levels of marine omega-3 fatty acids and the rate of telomere shortening over five years.[118]

Aspirin, ACE inhibitors and particularly statin therapy have been shown to positively impact on the vascular endothelium via anti-senescence effects. Over and above its anti-thrombotic and anti-inflammatory effects, aspirin has been shown to decrease the formation of dimethylarginine, an endogenous inhibitor of nitric oxide synthase, thereby reducing oxidative stress and delaying endothelial cell senescence.[119] ACE inhibitors, particularly those containing the sulfhydryl group, have been shown to delay endothelial cell senescence by activating Akt phosphorylation, increasing the expression of nitric oxide synthase and up-regulating telomerase.[120]

Several studies have suggested that the survival benefit attributed to statin therapy may be linked to its effects on telomere biology. Spyridopoulos *et al*. have shown that statins enhance the migratory capacity of endothelial progenitor cells by up-regulation of TRF2, the telomere-binding protein that stabilises telomere structure at the t-loop.[121] Satoh and co-workers demonstrated that intensive statin therapy over 12 months, through its anti-oxidant effects, prevents endothelial progenitor cell telomere erosion in patients with CAD.[122] A recent publication by Saliques *et al*. who studied patients presenting with acute myocardial infarction, showed that prior statin therapy was independently associated with significantly longer telomere length in subjects below the age of 64 years.[123]

Conclusion

Our interest in telomere biology stems from the high incidence of both premature CAD and type 2 diabetes mellitus witnessed in the population that we serve. Patients with CAD who have diabetes have worse outcomes than those without diabetes. This, coupled with the fact that the initial presentation in a substantial majority of our young patients is with myocardial infarction, which carries a worse prognosis than stable CAD, further contributes to adverse long-term outcomes. Indications are that revascularisation procedures are not as efficacious in this population.

The availability of quantitative polymerase chain reaction, which is a simpler, less labour-intensive and cheaper method requiring smaller quantities of DNA compared to the standard method of southern blot analysis, has made it feasible for us to determine telomere length in our patients.[124,125]

The study of telomere dynamics may serve several functions. Firstly, measuring telomere length in the early years of life may indicate a genetic predisposition and help target susceptible individuals. Studies on the genetic contribution to premature CAD with genome-wide association scans have yielded little thus far, whereas an assessment of telomere length provides a more universal insight into the genetics of CAD.

Secondly, telomere length is a measure of cumulative DNA damage from multiple environmental risk factors over an individual's lifespan

and is likely a better predictor of CAD than the currently available risk markers, which are single, point measurements in time.

Thirdly, although the development and progression of atherosclerosis occurs over decades, the process is clinically silent until the manifestation of full-blown disease. The rate of telomere shortening is accelerated prior to the onset of clinical disease, so longitudinal assessments of telomere length may be of predictive value. Finally, novel therapies aimed at delaying cellular senescence by manipulation of the telomere/telomerase complex may be of benefit.

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Blood glucose levels during acute illness can help predict future diabetes risk

Blood glucose levels measured in hospitalised patients during acute illness predicted the risk of developing type 2 diabetes in the following three years, according to a study published in *PLos Medicine* in August 2014.

Scottish researchers measured the blood glucose levels of 86 634 patients, aged 40 years or older, admitted for an acute illness between 2004 and 2008. Patients were followed up to December 2011 to determine their type 2 diabetes risk.

The researchers reported that type 2 diabetes risk for patients with a glucose level of less than 90 mg/dl (5 mmol/l) was 1% and the risk increased to approximately 15% among those with a glucose level of 270 mg/dl (15 mmol/l) or more. Plus, the risk of developing diabetes increased with increasing blood glucose levels during admission.

Based on the findings, the researchers developed a risk calculator that uses the patient's age, gender and admission blood glucose level to predict risk of developing diabetes over three years following hospital admission. However, the risk calculator has not yet been tested in non-white populations or populations outside of Scotland.

The researchers said in a press release, 'These findings can be used to inform individual patients of their long-term risk of type 2 diabetes and to offer lifestyle advice as appropriate.'

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Efficacy and safety of sirolimus-eluting stents versus bare-metal stents in coronary artery disease patients with diabetes: a meta-analysis

YANXIANG QIAO, YUAN BIAN, XIANLIANG YAN, ZHENFANG LIU, YUGUO CHEN

Abstract

Objective: **To compare by meta-analysis the efficacy and safety of sirolimus-eluting and bare-metal stents in coronary artery disease (CAD) patients with diabetes.**

Methods: **PubMed, MEDLINE and EMBASE were searched from 1971 to 2012. Data on the efficacy and safety of sirolimus-eluting and bare-metal stents in patients with diabetes were collected. A meta-analysis was then performed on a total of 1 259 CAD patients with diabetes from six studies. The odds ratio (OR) was used for comparison. Subgroup analysis was performed according to the sample size, year of study, subjects' geographic area and study method.**

Results: **Compared with those in the bare-metal stent group (BMS), the subjects in the sirolimus-eluting stent (SES) group had a reduced risk for major cardiac events [OR 0.42, 95% confidence interval (CI): 024–0.74, $p < 0.01$] and target-lesion revascularisation (OR 0.26, 95% CI: 0.11–0.59, $p < 0.01$). There was no difference for myocardial infarction (OR 0.92, 95% CI: 0.61–1.40, $p > 0.05$) or mortality (OR 1.19, 95% CI: 0.74–1.92, $p > 0.05$). Subgroup analysis showed a significant difference for overall risk of major cardiac events between SES and BMS when the sample size was ≤ 90 (OR 0.28, 95% CI: 0.16–0.48, $p < 0.01$), when it was a randomised control trial (RCT) (OR 0.28, 95% CI: 0.19–0.42, $p < 0.01$), or when it was performed on European subjects (OR 0.45, 95% CI: 0.27–0.77, $p < 0.01$). The sensitivity was not different when one study was removed at a time.**

Conclusion: **Our study confirmed that SES are safer and more effective than BMS in CAD patients with diabetes, as far as major cardiac events are concerned.**

Keywords: sirolimus-eluting stent, bare-metal stent, diabetes, meta-analysis, efficacy, safety

According to Nodari *et al*., compared to patients without diabetes, those with diabetes mellitus (DM) had increased cardiovascular morbidity and mortality, and were more likely to develop congestive heart failure (CHF).[1] Van Nunen used coronary stents for revascularisation in acute cardiac events and improved the prognosis, with a high success rate and favourable early outcome.[2]

The traditional bare-metal stent (BMS) was initially widely used, with considerable efficacy and safety. However, longterm outcome and restenosis rate has been very discouraging.[3] Recently, sirolimus-eluting stents (SES) have been increasingly used for treating restenosis after having used BMS, as well as for treating the native coronary narrowing.[4-7]

For coronary arterial disease (CAD) patients with diabetes, the outcome, efficacy and safety of SES and BMS remain controversial,[8-16] mainly due to small sample sizes or low statistical power. Meta-analysis, combining results of several studies and producing a single estimate of major events with enhanced precision, has been considered a powerful tool for summarising inconsistent results from different studies.[17-20] Heterogeneity and publication bias can be detected with funnel plots and other methodologies.[21-26]

To clarify this controversy, in this study, we performed a meta-analysis and subgroup analysis, along with heterogeneity and publication-bias analysis, and compared the major cardiac events, target-lesion revascularisation, myocardial infarction and mortality rate in CAD patients with diabetes who were treated with SES or BMS.

Methods

PubMed, MEDLINE, EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google scholar were searched. The following keywords were used, 'sirolimus-eluting stents', 'baremetal stents', 'coronary arterial disease', 'diabetes', 'diabetic', 'safety', 'efficacy', 'study' and 'trial'. The time period was limited from 1 January 1971 to 31 December 2012. The language published in was limited to English only. References of the articles were also checked for additional studies.

Studies included were randomised, controlled trials (RCT) and non-RCT conducted in coronary artery disease patients with diabetes treated with SES or BMS (studies with these two methods compared), regardless of the sample size. Excluded studies were those investigating patients with CAD or DM in only case reports or review articles, duplicated articles, and those with no comparison of SES and BMS.

After the investigators were trained, the data-mining form was developed and modified. The data included study details such as first author, year of study, year of publication, geographical area of subjects, demographics of subjects, and events with follow up after being treated with SES or BMS. According to the standard protocol, two investigators (A and B) mined the data independently, which was reviewed by the third one (C). Discrepancies were resolved through internal and external discussions (with the original investigators).

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S Afr J Diabetes Vasc Dis 2015; **12**: 62–67

Statistical analysis

Analysis was performed with software review manager 5.1 (Cochrane collaboration, http://ims.cochrane.org/revman) and comprehensive meta-analysis (Englewood, NJ); $p < 0.05$ was regarded as statistically significant. Meta-analysis was performed in fixed- or random-effect models.

Odds ratios (OR) and 95% confidence intervals (CI) were estimated in each study. Pooled ORs were obtained using the Mantel-Haenszel method in a fixed-effect model, and the DerSimonian-Laid method in a random-effects model.[24] The significance of pooled ORs was determined by the Z-test. Cochrane's *Q*-statistic was used to assess within- and betweenstudies variations. A $p < 0.10$ on the *Q*-statistic was regarded as heterogeneity across the studies. I^2 was also used to test heterogeneity with the formula:

$$I^2 = \frac{(Q - df)}{Q} \times 100\%$$

where $I^2 < 25\%$ means no heterogeneity; $I^2 = 25–50\%$ means moderate heterogeneity; $I^2 > 50\%$ means large or extreme heterogeneity.[27]

The random-effects model was also used for evaluating the possibility of heterogeneity of studies. Publication bias was evaluated with Egger's test and funnel plots,[28] which compensate for each other's drawbacks. If there is evidence of publication bias, the funnel plot is noticeably asymmetric. For the Egger's test the significance level was set at 0.05. Sensitivity analysis was also performed to test reliability of the results, by removing one study at a time and repeating the meta-analysis.

Results

As shown in Fig. 1, among 3 658 articles potentially relevant to the search terms (PubMed: 1 103; MEDLINE: 765; Springer: 650; Elsevier Science Direct: 880; Cochrane Library: 50; Google Scholar: 210), 323 potentially relevant studies were selected after the duplicates were removed. When the abstracts were screened 276 were excluded (65 were review articles, 156 were not diabetic patients, 55 did not report on BMS data). Among the remaining 47, another 41 were excluded (25 only reported on BMS data without comparisons, 16 were excluded due to unavailable data). Finally, six studies were included in this meta-analysis.

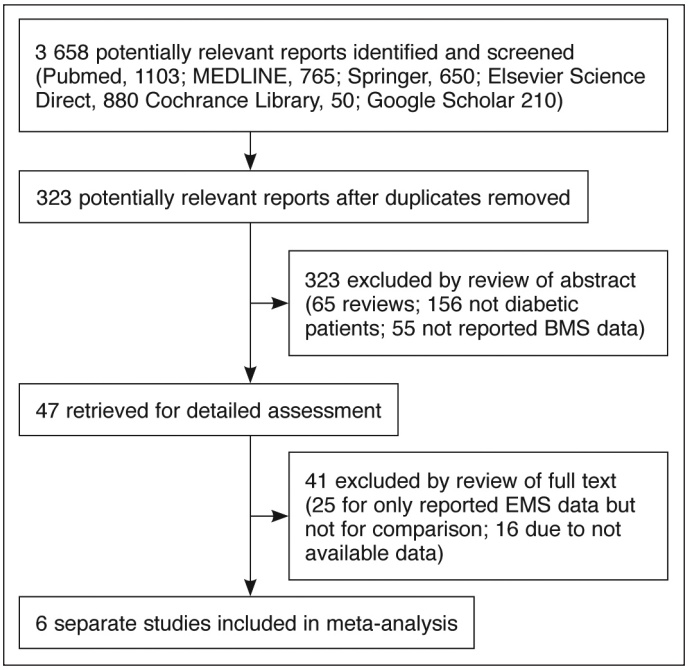


Figure 1. Flow chart of selection of the studies.

The characteristics of the included studies are presented in Table 1. These six studies were conducted from 2002 to 2006 and published between 2005 and 2008, three in Europeans, two in Americans, and one in Asians and Americans. A total of 1 259 CAD

Table 1. Characteristics of studies included in the meta-analysis

						SES group		BMS group	
Study	Study year	Country	Ethnicity	Study method	Follow up (years)	Sample size	Age (years)	Sample size	Age (years)
Aoki J, *et al.*	2002–2003	Netherlands	European	Non-RCT	1	112	63 ± 10	118	64 ± 11
Jimenez-Quevedo P, *et al.*	2003	United States	America	RCT	1	80	65.4 ± 8	80	67.9 ± 9
Baumgart D, *et al.*	2002–2004	Germany	European	RCT	1	94	66 ± 9	96	66 ± 10
Daemen J, *et al.*	2002–2003	United States	America	Non-RCT	1	206	62.0 ± 10	252	62.7 ± 10
Chan C, *et al.*	2002–2004	United States and Asia	America and Asian	RCT	1	54	58.7 ± 9.7	29	62.5 ± 10.3
Maresta A, *et al.*	2004–2006	Italy	European	RCT	1	68	71 ± 9	70	69 ± 9

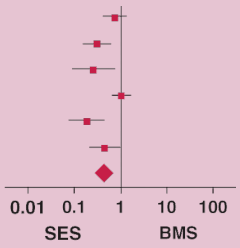
Table 2. Pooled odds ratio for the SES versus the BMS group

		Random model			Test of heterogeneity			Egger's test for publication bias	
Subgroups	No. of studies	OR (95% CI)	Z	*p* value	Q	*p*-value	I2 (%)	*t*	*p*-value
Overall effects	6	0.42 (0.24–0.74)	3.00	< 0.01	20.14	< 0.01	75.2	–4.19	0.014
Sample size ≤ 90	3	0.28 (0.16–0.48)	4.60	< 0.01	2.39	0.303	16.3	–3.66	0.62
Sample size > 90	3	0.61 (0.31–1.21)	1.42	0.15	8.70	0.013	77.0	–9.26	0.20
RCT	4	0.28 (0.19–0.42)	6.14	< 0.01	2.40	0.495	0.0	–2.36	0.531
Non-RCT	2	0.87 (0.61–1.24)	0.76	0.446	0.92	0.338	0.0	–5.29	–
European	3	0.45 (0.27–0.77)	2.95	< 0.01	3.71	0.156	46.1	–7.98	0.46
American and Asian	3	0.37 (0.11–1.27)	1.58	0.115	15.55	< 0.01	87.1	–5.92	0.23

A

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
Aoki J, *et al.*	27	112	37	118	18.5	0.70 (0.39–1.24)
Baumgart D, *et al.*	15	94	38	96	17.2	0.29 (0.15–0.58)
Chan C, *et al.*	8	54	12	29	12.8	0.25 (0.09–0.71)
Daemen J, *et al.*	44	206	54	252	20.1	1.00 (0.64–1.56)
Jimenez-Quevedo P, *et al.*	8	80	31	80	15.0	0.18 (0.07–0.41)
Maresta A, *et al.*	15	68	28	70	16.4	0.42 (0.20–0.90)
Total (95% CI)		614		645	100.0	0.42 (0.24–0.74)
Total events	117		200			

Heterogeneity: Tau² = 0.36; Chi² = 20.14, df = 5 (p = 0.001); I2 = 75%
Test for overall effect: Z = 3.00 (p = 0.003)



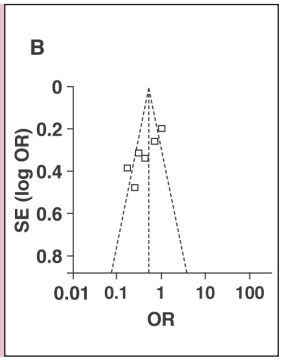


Figure 2. A: Forest plots of studies with major adverse cardiac events in the SES group versus the BMS group. B: Funnel plots of studies with major adverse cardiac events in the SES group versus the BMS group.

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
Aoki J, *et al.*	9	112	23	118	17.9	0.36 (0.16–0.82)
Baumgart D, *et al*	3	94	24	96	14.6	0.10 (0.03–0.34)
Chan C, *et al.*	7	54	10	29	15.7	0.28 (0.09–0.85)
Daemen J, *et al.*	28	206	35	252	19.9	0.98 (0.57–1.67)
Jimenez-Quevedo P, *et al*	5	80	28	80	16.4	0.12 (0.04–0.34)
Maresta A, *et al.*	4	68	21	70	15.5	0.15 (0.05–0.45)
Total (95% CI)		614		645	100.0	0.26 (0.11–0.59)
Total events	56		141			

Heterogeneity: Tau² = 0.83; Chi² = 24.44, df = 5 (p = 0.0002); I^2 = 80%
Test for overall effect: Z = 3.22 (p = 0.001)

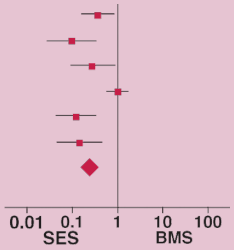


Figure 3. Forest plots of studies with target-lesion revascularisation events in the SES group versus the BMS group.

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
Aoki J, *et al.*	18	112	14	118	25.1	1.42 (0.67–3.02)
Baumgart D, et al.	4	94	5	96	10.4	0.81 (0.21–3.11)
Chan C, *et al.*	1	54	2	29	5.6	0.25 (0.02–2.94)
Daemen J, *et al.*	10	206	11	252	20.7	1.12 (0.47–2.69)
Jimenez-Quevedo P, *et al.*	2	80	6	80	12.8	0.32 (0.06–1.62)
Maresta A, *et al.*	11	68	14	70	25.4	0.77 (0.32–1.85)
Total (95% CI)		614		645	100.0	0.92 (0.61–1.40)
Total events	46		52			

Heterogeneity: Chi² = 4.37, df = 5 (p = 0.50); I^2 = 0%
Test for overall effect: Z = 0.37 (p = 0.71)

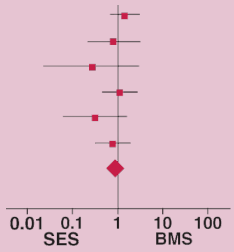


Figure 4. Forest plots of studies with myocardial infarction events in the SES group versus the BMS group.

subjects with diabetes (SES 614 and BMS 645) were included, with an average age of 65 years. The sample sizes ranged from 83 to 458, and the studies were RCTs and non-RCTs.

The efficacy of SES versus BMS is presented in Table 2. As shown, the pooled OR was 0.42 (95% CI: 0.24–0.74, $p < 0.01$) for SES versus BMS. This suggests that, after the data had been pooled, SES were more effective than BMS in CAD patients with diabetes. However, there was publication bias (t = –4.19, $p < 0.05$).

As shown in Fig. 2A, the pooled OR was 0.42 (95% CI: 0.24–0.74, $p < 0.01$) for overall events, suggesting that SES had a better outcome compared with BMS, with a greater reduction in risk for major cardiac events. However, there were heterogeneities between the studies (Q^2 = 20.14, I^2 = 75.0%, $p < 0.1$) and publication bias, as shown in Fig. 2B (asymmetric funnel plot). This was further confirmed with Egger's linear regression test, shown in Table 2 (t = –4.19, $p < 0.05$).

As shown in Fig. 3, the pooled OR was 0.26 (95% CI: 0.11–0.59, $p < 0.01$) for SES versus BMS, suggesting that SES had a better revascularisation rate for target lesions compared with BMS. However, there were heterogeneities between the studies (Q^2 = 24.44, I^2 = 80.0%, $p < 0.1$) and publication bias (t = –6.44, p < 0.05).

As shown in Fig. 4, the pooled OR was 0.92 (95% CI: 0.61–1.40, $p > 0.05$) for SES versus BMS, suggesting that the overall risk for myocardial infarction was not significantly different between these two groups. There was no heterogeneity between the studies (Q^2 = 4.37, I^2 = 0%, $p > 0.1$) but there was publication bias (t = –3.44, $p < 0.05$).

As shown in Fig. 5, the pooled OR was 1.19 (95% CI: 0.74–1.92, $p > 0.05$) for SES versus BMS, suggesting that the overall risk of mortality was not significantly different between the groups. There was no publication bias (t = –1.69, $P > 0.05$) or heterogeneities between the studies (Q^2 = 3.88, I^2 = 0.0%, $p > 0.1$).

Subgroup analyses were stratified by sample size, subjects' geographical area and study method. As shown in Table 2 and Figure 6A–C, the pooled OR was 0.28 (95% CI: 0.16–0.48, $p <$ 0.01, Fig. 6A) for SES versus BMS in studies whose sample size was

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
Aoki J, *et al.*	13	112	8	118	22.2	1.81 (0.72–4.54)
Baumgart D, *et al.*	5	94	3	96	12.1	1.29 (0.34–4.97)
Chan C, *et al.*	0	54	2	29	10.3	0.10 (0.00–2.18)
Daemen J, *et al.*	15	206	16	252	43.0	1.16 (0.56–2.40)
Jimenez-Quevedo P, *et al.*	1	80	2	80	6.4	0.49 (0.04–5.56)
Maresta A, *et al.*	3	68	2	70	6.1	1.57 (0.25–9.70)
Total (95% CI)		614		645	100.0	1.19 (0.74–1.92)
Total events	37		34			

Heterogeneity: Chi² = 3.88, df = 5 (p = 0.57); I^2 = 0%
Test for overall effect: Z = 0.72 (p = 0.47)

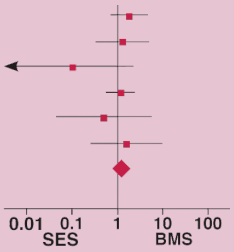


Figure 5. Forest plots of studies with mortality events in the SES group versus the BMS group.

above 90, with heterogeneities between the studies (Q^2 = 8.7, I^2 = 77%, p < 0.1). The pooled OR was 0.61 (95% CI: 0.31–1.21, p > 0.05, Fig. 6A) in studies whose sample size was 90 or less, without heterogeneities between the studies (Q^2 = 2.39, I^2 = 16%, p > 0.1).

The pooled OR was 0.45 (95% CI = 0.27–0.77, p < 0.01, Fig. 6B) in studies whose subjects were European, without heterogeneities between the studies (Q^2 = 3.71, I^2 = 46%, p > 0.1). The pooled OR was 0.37 (95% CI: 0.11–1.27, p > 0.05, Fig. 6B) in studies whose subjects were American and Asian, with heterogeneities between the studies (Q^2 = 15.55, I2 = 87%, p < 0.1).

The pooled OR was 0.28 (95% CI: 0.19–0.42, p < 0.01, Fig. 6C) in studies whose study method was RCT, without heterogeneities between the studies (Q^2 = 2.4, I2 = 0%, p > 0.1).

The pooled OR was 0.87 (95% CI: 0.61–1.24, p > 0.05, Fig. 6C) in studies whose method of study was non-RCT, without heterogeneities between the studies (Q^2 = 0.92, I2 = 0%, p > 0.1).

By removing one study at a time, a sensitivity analysis was performed and the model was rerun to determine the effect on each estimate. It showed that the above meta-analysis estimates did not change significantly after removal of each study, implying that these results were statistically reliable.

Discussion

A growing number of studies has shown the efficacy and safety of SES versus BMS for treating CAD patients with diabetes,[9,29] but the outcome has been controversial. In this analysis, we retrieved six studies, which included 1 259 CAD subjects with diabetes, and performed a meta-analysis. It showed that the SES group had a significant reduction in major adverse cardiac events, as well as target-lesion revascularisations, compared with the BMS group. There was no significant difference for myocardial infarction or mortality.

These results are consistent with a recent study that suggested a significant reduction in target-vessel revascularisations with SES, but with similar mortality rates.[9] Unlike this study, in which the incidence of myocardial infarction was higher, our analysis showed no difference for myocardial infarctions between the groups.

Another recent study conducted in Europeans confirmed the efficacy of SES compared with BMS, along with comparable mortality rates and myocardial infarctions,[11] which further proved the validity of our analysis. The efficacy and safety of SES have been receiving more and more supportive reports.[30-33] The uniqueness of our analysis and findings is that it proved the efficacy and safety of SES in CAD patients with diabetes.

A Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
6.2.2 Both groups' sample size > 90						
Aoki J, *et al.*	27	112	37	118	18.5	0.71 (0.39–1.24)
Baumgart D, *et al.*	15	94	38	96	17.2	0.29 (0.15–0.58)
Daemen J, *et al.*	44	206	54	252	20.1	1.00 (0.64–1.56)
Subtotal (95% CI)		412		466	55.8	0.61 (0.31–1.20)
Total events	86		129			
Heterogeneity: Tau² = 0.28, Chi² = 8.70, df = 2 (p = 0.01); I^2 = 77%						
Test for overall effect: Z = 1.42 (p = 0.15)						
6.2.3 Both groups' sample size ≤ 90						
Chan C, *et al.*	8	54	12	29	12.8	0.25 (0.09–0.71)
Jimenez-Quevedo P, *et al.*	8	80	31	80	15.0	0.18 (0.07–0.41)
Maresta A, *et al.*	15	68	28	70	16.4	0.42 (0.20–0.90)
Subtotal (95% CI)		202		179	44.2	0.28 (0.16–0.48)
Total events	31		71			
Heterogeneity: Tau² = 0.04, Chi² = 2.39, df = 2 (p = 0.30); I^2 = 16%						
Test for overall effect: Z = 4.60 (p < 0.00001)						
Total (95% CI)		614		645	100.0	0.42 (0.24–0.74)
Total events	117		200			

Heterogeneity: Tau² = 0.36, Chi² = 20.14, df = 5 (p = 0.001); I² = 75%
Test for overall effect: Z = 3.00 (p = 0.003)
Test for subgroup differences: Chi² = 3.12, df = 1 (p = 0.08); I^2 = 68.0%

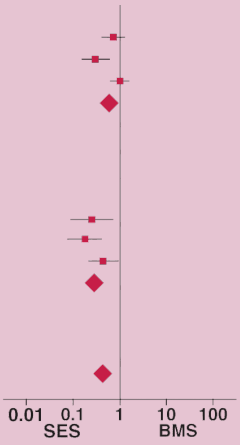
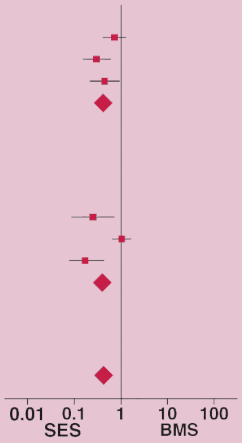


Figure 6. A: Forest plots of sample size subgroups

B

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
1.1.1 European Subgroup						
Aoki J, *et al.*	27	112	37	118	18.5	0.70 (0.39–1.24)
Baumgart D, *et al.*	15	94	38	96	17.2	0.29 (0.15–0.58)
Maresta A, *et al.*	15	68	28	70	16.4	0.42 (0.20–0.90)
Subtotal (95% CI)		274		284	52.1	0.45 (0.27–0.77)
Total events	57		103			
Heterogeneity: Tau² = 0.10, Chi² = 3.71, df = 2 (p = 0.16); I^2 = 46%						
Test for overall effect: Z = 2.95 (p = 0.003)						
1.1.2 American and Asian						
Chan C, *et al.*	8	54	12	29	12.8	0.25 (0.09–0.71)
Daemen J, *et al.*	44	206	54	252	20.1	1.00 (0.64–1.56)
Jimenez-Quevedo P, *et al.*	8	80	31	80	15.0	0.18 (0.07–0.41)
Subtotal (95% CI)		340		361	47.9	0.37 (0.11–1.27)
Total events	60		97			
Heterogeneity: Tau² = 1.02, Chi² = 15.55, df = 2 (p = 0.0004); I^2 = 87%						
Test for overall effect: Z = 1.58 (p = 0.11)						
Total (95% CI)		614		645	100.0	0.42 (0.24–0.74)
Total events	117		200			
Heterogeneity: Tau² = 0.36, Chi² = 20.14, df = 5 (p = 0.001); I² = 75%						
Test for overall effect: Z = 3.00 (p = 0.003)						
Test for subgroup differences: Chi² = 0.09, df = 1 (p = 0.77); I^2 = 0%						



C

Study or subgroup	SES Events	SES Total	BMS Events	BMS Total	Weight (%)	Odds ratio M–H, random, (95% CI)
5.1.1 RCT						
Baumgart D, *et al.*	15	94	38	96	17.2	0.29 (0.15–0.58)
Chan C, *et al.*	8	54	12	29	12.8	0.25 (0.09–0.71)
Jimenez-Quevedo P, *et al.*	8	80	31	80	15.0	0.18 (0.07–0.41)
Maresta A, *et al.*	15	68	28	70	16.4	0.42 (0.20–0.90)
Subtotal (95% CI)		296		275	61.4	0.28 (0.19–0.42)
Total events	46		109			
Heterogeneity: Tau² = 0.00, Chi² = 2.40, df = 3 (p = 0.49); I^2 = 0%						
Test for overall effect: Z = 6.14 (p = 0.00001)						
5.1.2 Non-RCT						
Aoki J, *et al.*	27	112	37	118	18.5	0.70 (0.39–1.24)
Daemen J, *et al.*	44	206	54	252	20.1	1.00 (0.64–1.56)
Subtotal (95% CI)		318		370	38.6	0.87 (0.61–1.24)
Total events	71		91			
Heterogeneity: Tau² = 0.00, Chi² = 0.92, df = 1 (p = 0.34); I^2 = 0%						
Test for overall effect: Z = 0.76 (p = 0.45)						
Total (95% CI)		614		645	100.0	0.42 (0.24–0.74)
Total events	117		200			
Heterogeneity: Tau² = 0.36, Chi² = 20.14, df = 5 (p = 0.001); I^2 = 75%						
Test for overall effect: Z = 3.00 (p = 0.003)						
Test for subgroup differences: Chi² = 16.81, df = 1 (p < 0.0010); I^2 = 94.1%						

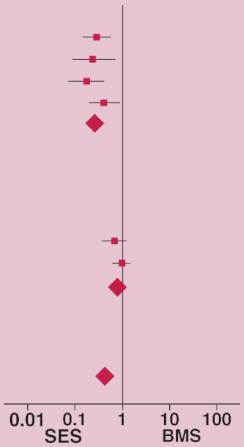


Figure 6. B: Forest plots of ethnicity subgroups. **C:** RCT or non-RCT subgroups.

Heterogeneity is one major concern with regard to the validity of meta-analyses.[26,34] Non-homogeneous data can easily give misleading results. In our study, the Q and I^2 statistics were performed to test heterogeneity. For all samples, there was significant heterogeneity for major adverse cardiac events in the SES and BMS groups.

We further conducted subgroup analysis according to sample size, ethnicity and study method. It demonstrated that in the studies where sample size was ≤ 90, method was a RCT and population was European, the overall major cardiac events were significantly different between the SES and BMS groups. Heterogeneity between the studies was decreased after stratifying the samples. No significant heterogeneity was observed with RCTs, suggesting an RCT is important for good results. More high-quality RCTs are therefore warranted.

Another concern for meta-analyses is publication bias, due to selection of the studies included. In this study, using funnel plots and Egger's test,[28,35,36] we found publication bias for overall major cardiac events, target-lesion revascularisations and myocardial infarction, but not for overall mortality. Furthermore, the sensitivity analysis confirmed there was no change if one study was removed at a time. Although more studies would have produced better results, overall, our results were statistically reliable.

Conclusion

This meta-analysis suggested that, compared with BMS, SES are more effective and safer for reducing major cardiac events in CAD patients with diabetes. This may indicate the direction for future trials and clinical implementation.

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Glycaemic, blood pressure and cholesterol control in 25 629 diabetics

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Abstract

Objective: **To examine and compare the extent to which people with type 2 diabetes (T2DM) are achieving haemoglobin A_{1c} (HbA_{1c}), blood pressure (BP) and LDL cholesterol (LDL-C) treatment targets.**

Methods: **A review of databases (MEDLINE Ovid, Pubmed and Sabinet) was performed and limited to the following terms: type 2 diabetes mellitus AND guideline AND goal achievement for the years 2009 to 2014 (five years).**

Results: **A total of 14 studies (25 629 patients) were selected across 19 different countries. An HbA_{1c} level of 7.0% (or less) was achieved by 44.5% of subjects (range 19.2–70.5%), while 35.2% (range 7.4–66.3%) achieved BP of 130/80 mmHg (or less), and 51.4% (range 20.0–82.9%) had an LDL-C level of either 2.5 or 2.6 mmol/l (100 mg/dl or less).**

Conclusion: **Despite guideline recommendations that lowering of HbA_{1c}, BP and lipids to target levels in T2DM will lead to a reduction in morbidity and mortality rates, we found that control of these risk factors remains sub-optimal, even across different settings.**

Keywords: type 2 diabetes mellitus, guidelines, goal achievement

Diabetes mellitus (DM) is a chronic, progressive condition leading to significant morbidity and premature death, and is an economic burden to any healthcare system. According to the International Diabetes Federation (IDF), there were 366 million people living with diabetes in 2011.[1] By 2035, it is predicted that more than half a billion people will have the disease.

Trends in urbanisation and the adoption of unhealthy Western lifestyles have begun to affect low- and middle-income countries (LMICs). A prime example of this is South Africa, which previously had the dubious pleasure of infectious diseases being the primary source of mortality. Today, expansion of non-communicable diseases (NCD) is beginning to manifest and deplete the already strained health resources available.[2]

Rather than being limited to glycaemia alone, the management of type 2 diabetes mellitus (T2DM) includes multiple priorities, including identification and treatment of other modifiable risk factors. It is widely accepted that T2DM is associated with cardiovascular disease (CVD) and increased mortality rates.[3]

In addition to lifestyle changes, the importance of reduction in levels of low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) has become an essential primary goal for the prevention of CVD in T2DM.[4,5] Furthermore, improved outcomes of diabetes-related chronic microvascular complications (retinopathy, neuropathy and nephropathy) are achieved through substantial reductions in incidence of both hyperglycaemia and hypertension. It is on the basis of this research that the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) recommends that most adults with diabetes should aim for an HbA_{1c} level of 7.0%, BP of 140/80 mmHg and LDL-C level of 2.5 mmol/l or less.[6]

There are many gaps in the management of T2DM that are proving difficult to close. Studies have revealed how clinical practice differs from clinical trials in that T2DM patients often cannot reach guideline-recommended targets. One of the ways to improve clinical outcomes is by comparing the performance of one clinical setting against another. In this study, our aim was to compare the achievement of the critical quality indicators: glycaemic, BP and lipid control in T2DM patients from different countries worldwide, in an attempt to benchmark which approach has been most successful.

Methods

This study was a literature review using Ovid MEDLINE, Pubmed and Sabinet databases. Studies included were those conducted in the past five years (2009–2014) and limited to the following key terms: type 2 diabetes mellitus AND guideline AND goal achievement (HbA_{1c}, glycated haemoglobin, blood pressure, systolic, diastolic, lipids, cholesterol, LDL cholesterol). We also reviewed a selected number of reference lists of other reviews and hand-searched several medical journals.

Studies that reported achievement of guideline-recommended targets of major risk factors for T2DM were included. The primary objective of this review was to provide an overview of achievement of major risk-factor targets (HbA_{1c}, BP and LDL-C) in the treatment of a sample of T2DM patients from different parts of the world. Specifically, the objectives would be addressed through comparison of the achievement of HbA_{1c}, BP and LDL-C targets, according to local or international guidelines, across different study samples.

The following data were extracted from the studies: author details, year of publication, study location, cohort size and achievement of major risk factors (combined systolic and diastolic BP, and HbA_{1c} and LDL-C levels). As different samples of study countries followed different guideline targets, flexibilities around these differences was needed. Studies selected for this article may have differed in the following parameters: recruitment and randomisation methods,

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S Afr J Diabetes Vasc Dis 2015; **12**: 68–71

total number of study participants recruited, study sites (e.g. single or multicentre), gender ratios, ethnicity ratios, timelines of results presented (e.g. single or longitudinal data) and periods of enrollment.

To compare results, we standardised (or converted or conformed) certain measurement units in order to maintain consistency (e.g. LDL-C in mmol/l instead of mg/dl). The control or baseline results of studies were reported instead of interventional group data. Only the latest data were selected from studies with multiple time periods.

Studies excluded from the review had one or more of the following characteristics: non-English language, studies conducted before 2009, participating patients younger than 18 years of age, participants reported to have had any diabetes other than T2DM (e.g. gestational, type 1 or steroid induced), studies that reported insufficient data or less than two of the three major risk factors being compared, and studies that consisted of large HMO claims databases. The latter was chosen as an exclusion criterion as larger-sized cohort studies would have biased the results of this review.

Data presented in this article were collected from the results of other studies and are limited to the authors' definitions of control. This review did not allow for the access of patient-level data of different studies included in the review to be accessed. It was assumed that all data extracted for this study were collected from the medical records of patients who willingly participated in the studies included in this review. The relevant data were captured into a secure database using Microsoft Excel 2010. Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical).

Results

The authors of this study set out to determine how diabetes care compared across different settings, given the healthcare challenges faced especially by under-resourced areas. Of the 511 (154 from Ovid MEDLINE + 32 Pubmed + 325 Sabinet) titles initially identified between 2009 and 2014, 14 studies fulfilled the inclusion criteria. These 14 studies originated from 19 different countries (some studies included more than a single country) and we enrolled a total of 25 629 patients.

There were 17 high-income, one upper-middle- (South Africa) and one low-income (Uganda) country included in the review (grouped according to the United Nations' economies by per-capita country classification).[7] Cohort sizes ranged from 50 to 4 926 patients. Twelve studies contained results for all major risk factors (HbA_{1c}, BP and LDL-C), while the rest included at least two-thirds of the measured risk factors. There were eight studies (57.1%) that defined treatment targets as per the American Diabetes Association.[8] The characteristics of each study are outlined in Table 1.

In 12 studies (25 354 patients) that used an HbA_{1c} level of 7.0% or less to define control, 44.5% (range 19.2–70.5%) of patients achieved target.[9-20] In two studies (275 patients) where HbA_{1c} level was defined as < 6.5 and < 8.0%, respectively, 56.6 and 60.0% of patients reached their targets, respectively.[21,22]

In eight studies (18 089 patients), which had the definition of target BP of 130/80 mmHg or less (systolic and diastolic combined), 35.2% (range 7.4–66.3%) of patients achieved target.[9-11,16-19,21] In four studies (7 240 patients) where systolic BP targets of 130 mmHg or less (alone) defined control, 32.7% (range 21.3–50.0%) of the subjects achieved target.[12,13,15,20] In two studies (300 patients) with a BP target of either < 140/90 or < 140/80 mmHg, 24.0 and 56.0% of patients achieved goal, respectively.[14,22]

Table 1. Study characteristics

First author (reference)	Year of publication	Location	Cohort size (n)	Achievement of target: HbA_{1c} (< 7%)	BP (< 130/80 mmHg)	LDL-C (< 2.6 mmol/l)
Al-Taweel[9]	2013	Kuwait	652	19.2	46.0	–
Braga[10]	2012	Canada	3002	52.6	53.6	64.2‖
Casagrande[11]	2013	USA	4926	52.5	51.1	56.2
Goderis[12]	2009	Belgium	2495	54.0	50.0‡	42
Hermans[13]	2013	Belgium, Greece, Luxembourg, Portugal, Spain, UK	3996	49.2	27.3‡	40.8
Kibirige[14]	2014	Uganda	250	20.8	56.0§	20.0
Klisiewicz[15]	2009	South Africa	150	30.7	21.3‡	50.7‖
Lee[16]	2009	Korea	926	49.2	66.3	51.0
Morren[21]	2010	Trinidad	225	56.6†	53.6	49.3**
Pinchevsky[17]	2013	South Africa	666	26.2	45.8	53.8‖
Sease[18]	2013	USA	95	35.8	62.1	82.9
Stone[19]	2013	Belgium	1044	59.7	27.6	49.7
Stone[19]	2013	France	1056	65.3	14.9	52.4
Stone[19]	2013	Germany	959	48.6	7.4	30.7
Stone[19]	2013	Ireland	950	53.4	24.9	76.9
Stone[19]	2013	Italy	984	35.7	20.8	40.4
Stone[19]	2013	Netherlands	1021	70.5	20.3	58.9
Stone[19]	2013	Sweden	550	56.5	27.1	47.3
Stone[19]	2013	UK	1033	39.1	25.0	74.5
Umar-Kamara[22]	2011	USA	50	60.0*	24.0¶	–
Webb[20]	2014	South Africa	599	27.0	32.0‡	33.0‖

Exceptions to the above targets are indicated by the following:
†HbA_{1c} < 6.5%; *HbA_{1c} < 8.0%;
‡systolic blood pressure only < 130 mmHg;
§systolic/diastolic blood pressure < 140/80 mmHg; ¶systolic/diastolic blood pressure < 140/90 mmHg;
‖low-density lipoprotein cholesterol < 2.5 mmol/l;
**total cholesterol < 5.18 mmol/l.

In the 11 studies (24 702 patients) that used LDL-C levels of either 2.5 or 2.6 mmol/l (100 mg/dl or less) to define control, 51.4% (range 20.0–82.9%) of patients achieved goal.[10-20] One study (225 patients) with a total cholesterol target of < 200 mg/dl (5 mmol/l) had 49.3% of patients at goal.[21] Two studies (702 patients) did not measure lipid levels.[9,22]

In general, more patients reached target for LDL-C than for HbA_{1c} levels, with the poorest achievement of targets being BP. The widest variability of target achievement was LDL-C (variation of 62.9%), followed by BP and then HbA_{1c} (least variability). The highest and lowest achieved targets were those by an American (LDL-C, 82.9%) and a German study (BP, 7.4%), respectively.[18,19]

Discussion

The quality of diabetes care cannot simply be measured across proportions of patients achieving guideline targets. However, a broad overview of the quality of care can be gauged when comparing target adherence across different countries, especially with adequately sized samples of patients. Hence the reason for this review, where countries from various economies were compared, according to achievement of modifiable risk factors against the guidelines. Based on the results of other studies, this review set out to establish the achievement of major risk-factor targets (HbA_{1c}, BP and LDL-C levels) in the treatment of DM patients in different parts of the world.

Given the increasing prevalence of T2DM, effective management of critical diabetes risk factors can significantly contribute towards improved outcomes. Attaining targets requires improved methods to increase adherence to lifestyle (exercise/diet) and pharmacological interventions. From this review, it was evident that certain studies appeared to be more successful at managing patients' risk factors than others.

Practitioners achieving better guideline adherence should be encouraged to share their management strategies for implementation with other healthcare facilities. Hermans *et al.* found that by benchmarking the level of care of 'three paramount cardiovascular risk factors' in a primary care setting has in itself led to a clinically significant improvement in T2DM care over time.[13] There is also evidence to suggest that performance with regard to management of a disease, when compared between a physician and his/her colleagues, has brought about an intellectual, emotional and competitive incentive for change.[23]

The most critical ways of reducing T2DM complications is by collectively managing HbA_{1c}, BP and LDL-C levels. More patients achieved LDL-C than HbA_{1c} targets in the studies reviewed, potentially owing to the progressive nature of the disease, where β-cell function gradually declines over time. BP control was the least-achieved risk factor across all the studies, and according to McLean *et al.*, may have occurred due to the 'inadvertent under emphasis' of treating T2DM-associated risk factors (such as hypertension, when there is strong emphasis on glucose control).[24] Perhaps it was due to inadequate dosages, poor adherence to medication, poor access to follow-up care or a combination of these. A well-designed, randomised, controlled trial may help address these questions.

Once considered rare in sub-Saharan Africa, the prevalence of T2DM is rapidly increasing. As many as four out of every five diabetics reside in LMICs, many of whom remain undiagnosed.[1] T2DM is a complex, resource-intensive disease requiring multifactorial yet individually tailoured, lifelong treatment.

Most of the studies found and included in this review were from higher-income countries. However patterns of poor control rates were common across all settings. For instance, less than 40% of patients from the USA, Europe (specifically Italy) and the UK studies (all high-income countries) achieved HbA_{1c} levels (< 7%) comparable with those of lower- to upper-middleincome countries (Uganda and South Africa, respectively).[14,17-20] Similarly, the combined results of six European countries, and other individual studies, had less than half of patients at LDL-C target, as seen in two separate non-high-income countries.[13,14,20] Yet on the other hand, and possibly as expected from moredeveloped nations, two to three times more patients from separate European (specifically the Netherlands) and a USA study achieved HbA_{1c} (< 7%) and LDL-C (< 2.6mmol/l) targets in comparison with a lower-income country, respectively.[14,19,22]

The differences across the sites in their abilities to achieve guideline targets may be attributed to socio-economic reasons. In resource-rich settings, where patients supposedly receive the extra time required for diabetes care through more regular physician interactions or appointments, appropriate reminder systems and adherence monitoring, this may improve the standards of diabetes care received. Lower-income countries face the realities of inadequate healthcare infrastructure, regular medication stock outs, few educational programmes and minimal healthcare facilities/professionals.[25] This literature review covered the influences of multiple background factors occurring across healthcare systems in different countries, hence the differences in targets achieved across the environments studied.

As described above, Africa faces many healthcare challenges, both within and between countries. Despite resource constraints, by targeting the modifiable risk factors associated with DM, there is still the potential for improvement, and better patient outcomes. This review serves to highlight the proportion of patients achieving guideline targets across different settings. The aim of this review was to serve as a benchmark for those countries selected, in order to measure their performance against each other in terms of achieving guideline targets.

By recognising those healthcare settings with increased patient numbers achieving guideline targets, this could allow for future studies to identify the mechanisms and processes used to achieve their targets. Areas of interest for the improvement of diabetes care could include: organisational characteristics such as improved implementation of adherence to clinical guidelines (evidence-based), identification of individuals to act as guideline champions to deliver more performance measures, and feedback to healthcare providers on progress made. Perhaps, once identified, the settings achieving less-favourable control of modifiable risk factors may begin to explore approaches used in the more successful settings. In addition, given the chronic progressive nature of DM, it is hoped that attention will be prioritised not just on treatment but also on prevention strategies in those settings wishing to improve their level of diabetes care offered.

It has been predicted that the ageing populations of LMICs will face a significant increase in mortality rate due to NCDs over the next 25 years.[26] Although not included in this review, a previous South African study revealed that only 30.4% of the 899 patients achieved HbA_{1c} levels < 7%, which is similar to the three studies included in this review from the same locale.[27] The three South African studies included in this review had noticeably fewer patients at HbA_{1c} goal in comparison with other countries. One of the reasons for this may have been that all the South African studies included in this review were from the public sector, which has often been described as 'overburdened', and due to resource constraints, cannot always offer appropriate levels of healthcare or access to the most modern of diabetes treatments currently available in South Africa's private sector or in those high-income countries included in this study. Furthermore, many of the patients serviced in South Africa's public sector settings originate from a lower socioeconomic background, which may indicate lower educational levels or limited access to healthier lifestyle choices. Perhaps HbA_{1c} level is still the most challenging of risk factors to control, especially in less-developed economies.

Study limitations

Studies included in this review differed with regard to guidelines or targets, however, we tried to overcome this by consistently capturing and comparing similar risk factors using standardised

units. Patients selected for the studies included in the review were treated to 'moving targets' and therefore studies conducted in the past five years only (2009–2014) were included, as recent guidelines have more similar targets.

Some eight out of the 14 studies provided information on the type of methods used for clinical and laboratory-based measurements, but with differing levels of detail. Notably, only two studies confirmed use of DCCT-standardised laboratory analysers for HbA_{1c} analysis. By converting to similar units (e.g. LDL-C from mg/dl to mmol/l), target values in this retrospective study (Table 1) were presented in a format that would allow for comparison. Ideally, a centralised laboratory should have been used for measurements included in this study, however, we relied on previously obtained measurements from other studies. We therefore cannot guarantee the accuracy or precision of measurements in the studies selected for this review, as methodologies may have differed. Studies from resourcerich settings may have implemented newer, more sophisticated and improved methods for A_{1c} and LDL-C measurements, influencing the results of those specific studies.

This review did not stratify the selected individual studies according to patient profiles, severity of disease, clinical settings (clinic or hospital) or involvement of specialists (factors affecting how individuals are managed and able to reach guideline targets). Although smoking is considered a critical risk factor in the prevention and management of CVD, it was not included as a crucial study parameter for this review (partly due to many studies not reporting this).

Although previously identified as a source of bias, we only included studies published in English, which according to an analysis, has little effect on summaries of treatment effect estimates.[28] Publication bias may have occurred in our study in that a single reviewer (author) carried out the searches without the use of specific methodology (e.g. Cochrane data system).

Conclusion

The results presented in this study demonstrate that T2DM patients remain inadequately controlled for their cardiovascular risk factors. Our review revealed that control of major risk factors did not differ significantly between countries or healthcare settings. There is substantial room for improvement in the way T2DM patients are being managed for their condition. Further efforts through multidisciplinary action to improve guideline adherence is critical for the prevention or delay of diabetesrelated complications.

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Prevalence and covariates of electrocardiographic left ventricular hypertrophy in diabetic patients in Tanzania

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Summary

Background: **Left ventricular hypertrophy (LVH) has been demonstrated to be a powerful predictor of cardiovascular (CV) morbidity and mortality in diabetic as well as hypertensive patients. However, less is known about the prevalence of electrocardiographic LVH (ECG-LVH) and its relation to other CV risk factors in diabetic patients in sub-Saharan Africa. Therefore, the aim was to assess the prevalence of ECG-LVH in diabetic patients in Dar es Salaam, Tanzania, and its relation to other cardiovascular risk factors.**

Methods: **Two hundred and thirty-seven consecutive patients attending the Muhimbili diabetic clinic were studied. ECG-LVH was diagnosed by Sokolow-Lyon voltage and Cornell voltage-duration product criteria. Q waves, ST-segment deviation, T-wave abnormalities and intraventricular conduction defects were classified by the Minnesota codes. Blood pressure (BP), serum creatinine, cholesterol and triglyceride levels, and HbA_{1c} and urinary albumin and creatinine concentrations were determined.**

Results: **The prevalence of LVH in patients was 16% by either ECG criteria; 12.2% by Sokolow-Lyon and 5.1% by Cornell product criteria. Patients with LVH had significantly higher systolic and mean BP and pulse pressure, and a higher prevalence of ST-segment abnormalities, T-wave inversion and albuminuria than those without LVH (all $p < 0.05$). In multivariate logistic regression analysis, systolic BP was the only independent predictor of ECG-LVH. The prevalence of ECG-LVH increased by 15% per 10 mmHg higher systolic BP [OR 1.151 (95% CI 1.009–21.314), $p < 0.05$]. Clustering of cardiovascular risk factors differed significantly between type 1 and type 2 diabetes patients. On average, type 1 patients had 0.8 and type 2 had 2.2 additional CV risk factors.**

Conclusion: **ECG-LVH was present in 16% of diabetic patients in Tanzania. Systolic BP was the most important predictor of ECG-LVH. Clustering of CV risks was significantly higher in type 2 than in type 1 diabetics, demonstrating the need for systematic multiple risk-factor assessment in these patients.**

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Left ventricular hypertrophy (LVH), whether diagnosed by electrocardiography or echocardiography, is a manifestation of cardiac target-organ damage and has been demonstrated to be a powerful predictor of cardiovascular morbidity and mortality in diabetic[1,2] as well as hypertensive patients.[3,4] Physiologically, LVH is a structural and functional adaptation of the left ventricle chamber to increased afterload. In previous studies, main determinants of ECG-LVH, including advanced age,[5] male gender,[6,7] obesity,[8,9] glucose intolerance, diabetes mellitus, lipid abnormalities, cigarette smoking and microalbuminuria[10] have been identified.

ECG-LVH has particularly been associated with hypertension in African patients.[11-13] However, less is known about prevalence of electrocardiographic left ventricular hypertrophy (ECG-LVH) and its relation to other cardiovascular (CV) risk factors in diabetic patients in sub-Saharan Africa. Therefore, the aim of the present study was to assess the prevalence of ECG-LVH and its relation to other CV risk factors in diabetic patients attending the diabetes outpatient clinic at the Muhimbili National University Hospital in Dar es Salaam.

Methods

All 290 patients attending the diabetes outpatient clinic at Muhimbili National Hospital between 1 August 2003 and 1 February 2004 were invited to participate in the study. All 271 patients without cardiac or renal failure, cerebral vascular disease or advanced liver disease were invited; 263 accepted participation in the present study. Muhimbili Hospital is the national referral and a university teaching hospital. All patients gave written informed consent before enrolment in the study.

The study was approved by the Scientific and Publication Committee of Muhimbili University College of Health Sciences and the Regional Ethical Committee III in Norway. The study was conducted in accordance with the Helsinki declaration. Patients were classified as type 1 or type 2 diabetics according to the 1997 World Health Organisation (WHO)[14] clinical criteria, based on age at diagnosis, mode of onset (acute versus insidious presentation), duration of disease, current treatment, body mass index (BMI), waist-to-hip ratio, blood pressure, random or fasting glucose, HbA_{1c} and urine ketone levels.

Patients aged 30 years or younger at onset of diabetes, with acute presentation of classical symptoms, who required insulin therapy to control hyperglycaemia were classified as type 1. Patients older than 30 years who needed insulin treatment, even if they had had diabetes for a short duration, or were metabolically uncontrolled and/or underweight, were also classified as type 1.

Patients over 30 years at diagnosis and not needing insulin for metabolic control were classified as type 2 diabetics. Patients younger than 30 years were also classified as type 2 if they were obese and/or had diabetes duration of more than 10 years without

the need of insulin treatment. Patients not fitting into the clinical features of either type were classified as undetermined and excluded from the present analysis.

All patients completed a questionnaire on demographics and CV history including smoking behaviour, presence of hypertension and use of antihypertensive drugs. Clinic blood pressure was measured in the supine position using a calibrated mercury sphygmomanometer after at least half an hour of rest in a quiet room. The systolic BP (SBP) was recorded at Korotkoff phase one and diastolic BP (DBP) at phase five. Blood pressure was measured twice within an interval of five to 10 minutes; the second measurement was taken as the clinic BP.

Body weight was measured to the nearest 0.5 kg and height to the nearest 0.5 cm. Body mass index was calculated as weight (kg)/height (m^2) and categorised according to the WHO physical status interpretation.[15] Patients with a BMI of ≤ 18.5 kg/m^2 were regarded as underweight, those with a BMI of 18.5–24.9 kg/m^2 as normal, 25.0–29.9 kg/m^2 as overweight and those ≥ 30 kg/m^2 as obese. Waist and hip circumferences were measured in centimetres and the waist-to-hip ratio (WHR) was calculated. Waist circumference (WC) was measured to the nearest 0.1 cm, at the midway point between the lowest rib and the iliac crest, at minimal respiration. Men with WC above 102 cm (40 inches) and women with WC above 88 cm (35 inches) were considered to have abdominal obesity.[16]

Electrocardiogram

A resting, standard 12-lead ECG was obtained in all patients in a supine position in a quite room. Recording was done at a speed of 25 mm/sec and calibration was standardised at 10 mm/mV on a Schiller electrocardiograph Cardiovit AT-1 (Schiller AG, model No: SHL41, Altgasse 68, CH-6341 Baar, Switzerland).

The rhythm was read from the rhythm strip obtained from lead V1. The rhythm was classified as sinus rhythm, atrial fibrillation or other. Left ventricular hypertrophy was diagnosed by Sokolow-Lyon voltage criterion (the sum of the amplitude of the S wave in lead V1 or V2 and R wave in lead V5 or V6, in both genders) and Cornell voltage-duration product criterion (the sum of the amplitudes of the R wave in lead aVL and S wave in lead V3, adding 6 mm in women, and multiplied by the QRS duration). LV hypertrophy was considered present if the Sokolow-Lyon voltage criterion was above 35 mm,[17] or if the Cornell voltage-duration product criterion was above 2 440 mm/ms. 18-21 Q waves, (code 1-1), ST-segment deviation (codes 4-1 to 4-4), T-wave abnormalities (codes 5-1 to 5-4) and intraventricular conduction defects (codes 7-1 to 7-8) were classified using the Minnesota codes.[22]

Blood and urine analysis

Blood samples were drawn from the antecubital vein, centrifuged and stored at –80°C until shipped to the central clinical laboratory at the Haukeland University Hospital in Bergen, Norway. Samples were analysed on a Modular Analytics SWA auto analyser (Roche Diagnostics GmbH, 68298 Mannheim Germany) using kits produced by Boehringer Mannheim (Mannheim, Germany). Serum and urine creatinine were analysed using a modified kinetic method of the Jaffé reaction, serum cholesterol was assessed on cholesterol oxidase paminophenazone (CHOD-PAP) levels, and serum triglycerides by the glycerol phosphate oxidase p-aminophenazone (GPOPAP) method.

Capillary blood glucose (fasting or random), haemoglobin (Hg) and HbA_{1c} levels were measured in Dar es Salaam. Capillary blood glucose was measured on a HemoCue AB glucose analyser (Angelholm, Sweden), haemoglobin on a HemoCue analyser and HbA_{1c} was assessed by DCA 2000®+ (Bayer Corporation). The DCA 2000®+ was standardised against the DCCT method and verified in 1996.[23] Quality control was maintained using standardised solutions.

Urine analysis was done on two overnight specimens collected on two separate days. Samples were screened for features of urinary tract infection and excluded if present. Urine albumin concentrations were determined using an automated immunoturbidity assay with a sensitivity of 2.3 mg/l and inter- and intra-assay coefficients of variation of 4.4 and 4.3%, respectively. A urinary albumin excretion rate (AER) of ≤ 20 µg/min was categorised as normoalbuminuria, 20.1–200 µg/min as microalbuminuria and AER levels of > 200 µg/min as macroalbuminuria.

Cardiovascular risk factors

The CV risk factors in this study were assessed and defined as described by the 1999 WHO/ISH guidelines.[24] These included waist circumference, hypertension, ECG-LVH, albuminuria, advanced age, smoking, dyslipidaemia and albuminuria. Waist circumference was chosen as the indicator variable for abdominal obesity as it has been established to be a better predictor of cardiovascular health risks than BMI.[25] Subjects were considered to be hypertensive when the clinic blood pressure was ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic, or when using antihypertensive treatment.[26] Advanced age was defined as age over 55 years for men and over 65 years in women. Dyslipidaemia was defined as total cholesterol levels of above 6.5 mmol/l and/or LDL cholesterol above 4.0 mmol/l, and/ or HDL cholesterol below 1.0 mmol/l for men and below 1.2 mmol/l for women. Albuminuria was considered present if AER ≥ 20 µg/min. Diagnosis of ECG-LVH has been described in detail above.

Statistical analysis

This was performed using the statistical package for social sciences (SPSS) software, version 13 for windows (SPSS, Inc, Chicago, Illinois). Continuous data are reported as mean ± two standard deviations and categorical data as proportions. For variables with skewed distribution, which were age, diabetes duration, systolic and diastolic BP, AER and creatinine clearance, the median ± range was used. Patients were grouped according to type of diabetes.

Groups were compared using the unpaired t-test, Fisher exact test and Mann-Whitney test where appropriate. A logistic regression analysis test was used to quantify the association between covariates and the presence of ECG-LVH. In regression analysis, results are given per 10 mmHg higher systolic BP, per 5 mmHg higher diastolic BP and per 40 msec longer QRS duration for meaningful clinical interpretation. Results of regression analyses are given as odds ratio (OR) with 95% confidence interval (CI). A two-tailed p-value less than 0.05 was considered statistically significant in univariate and multivariate analyses.

Results

Two hundred and seventy-one patients were enrolled. Of these, 54.3% were women; six patients did not complete the study and were excluded, with 263 patients remaining. In 14 patients, the type of diabetes could not be clearly determined and they were excluded from the present study population, as were 12 patients (six type 1 and six type 2) who did not have an ECG taken. In the

Table 1. Demographic characteristics and the ECG findings in the study population divided by type of diabetes

Variables	Type 1 diabetes	Type 2 diabetes
Number (%)	89 (37.6)	148 (62.4)
Age at inclusion (years)	20.8 (4–45)	51.8 (23.5–85)***
Women, *n* (%)	44 (49.4)	83 (56.1)
Diabetes duration (years)	3.0(0–17)	4 (0–25)*
Smoking, *n* (%)		
Current smoker	2 (2.4)	4 (2.7)
Ex-smoker	1 (1.2)	25 (17)
Never smoked	82 (96.5)	118 (80.3)
BMI (kg/m^2)	19.4 (3.9)	27.8 (4.7)***
Waist circumference (cm)	70.3 (13.2)	94.2 (14.5)***
Waist–hip ratio (cm)	0.86 (0.73)	0.94 (0.11)***
Proportion with hypertension, *n* (%)	9 (11.7)	78 (54.2)***
ECG findings		
Any LVH criteria	14 (15.7)	23 (15.5)
Sokolow-Lyon voltage LVH	14 (15.7)	15 (10.1)
Cornell voltage-duration product LVH	0	12 (8.1)**
T-wave inversion	30 (33.7)	38 (25.7)
ST abnormality	13 (14.6)	18 (12.2)
Intraventricular conduction defects	8 (9.0)	38 (26)***

Data expressed as median (min–max) and mean (SD) as appropriate.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

final study population consisting of 148 type 2 and 89 type 1 diabetics, type 2 patients were significantly older ($p < 0.001$), had longer duration of diabetes ($p < 0.05$), higher body mass index ($p < 0.001$), waist circumference and waist-hip ratio ($p < 0.001$), and included more patients with hypertension (Table 1).

Prevalence of ECG-LVH

In the total study population, 37 (15.6%) patients had LVH by either Sokolow-Lyon or Cornell product criteria. The prevalence of ECG-LVH by the Sokolow-Lyon criterion was 12.2% of patients in the total study population, and by the Cornell product criterion 5.1%. The prevalence of LVH by any criteria did not differ between type 1 and type 2 patients (15.7 vs 15.5%, ns) (Table 1).

All type 1 patients with LVH were identified by the Sokolow-Lyon voltage criterion. Among the 23 type 2 diabetic patients with ECG-LVH, 12 were identified by the Cornell voltage product criterion and 15 by the Sokolow-Lyon voltage criterion. Four patients were identified by both criteria. Sixteen (44.4%) hypertensive patients and 11 (29.7%) patients with albuminuria had ECG-LVH identified by either the Cornell voltage product criterion or the Sokolow-Lyon voltage criterion.

Covariates of ECG-LVH

Type 2 patients with ECG-LVH by either criterion had significantly higher systolic and mean BP than patients without ECG-LVH (Table 2). There were, however, no differences between all the covariates in type 1 patients with or without ECG-LVH. In logistic regression analysis in type 2 patients of both genders, with diabetes type, age, diabetes duration, waist circumference, systolic and diastolic BP and albuminuria as the independent variables, ECG-LVH was associated with albuminuria [OR 4.046 (95% CI, 1.517–10.796), $p < 0.01$], and higher systolic BP [OR 1.534 per 10 mmHg higher SBP (95% CI, 1.081–2.176), $p < 0.01$] in univariate analysis.

Including the significant variables in a multivariate model, systolic BP was the only independent risk factor for ECG-LVH. The risk of

Table 2. Cardiovascular risk factors and biochemical characteristics in study patients with and without ECG-LVH

	Type 1 diabetes		Type 2 diabetes	
Variables	**No LVH**	**LVH by any criteria**	**No LVH**	**LVH by any criteria**
Basic characteristics *n* (%)	75 (84.3)	14 (15.7)	125 (84.5)	23 (15.5)
Women, *n* (%)	38 (86.4)	6 (13.6)	70 (84.3)	13 (15.7)
Body mass index (kg/m^2)	19.5 (4.1)	19.4 (2.5)	27.9 (4.6)	27.7 (5.4)
Waist circumference (cm)	69.7 (14)	74 (6.4)	95.1 (12.3)	94 (12.4)
Proportion with abdominal obesity *n* (%)	38 (88.4)	5 (11.6)	31 (93.9)	2 (6.1)
Blood pressure				
Systolic BP (mmHg)	103 (72–140)	110 (100–140)	134 (98–210)	150 (90–200)*
Diastolic BP (mmHg)	73 (50–110)	78 (50–83)	84 (60–120)	86 (68–136)
Mean BP (mmHg)	84 (12)	88 (8)	102 (15)	110 (20)*
Pulse pressure (mmHg)	35 (9)	41 (17)	53 (16)	61 (22)
Proportion with hypertension, *n* (%)	7 (77.8.)	2 (22.2)	59 (81.9)	13 (18.1)
Heart rate (bpm)	83 (17)	82 (15)	76 (15)	78 (10)
Biochemistry				
Total cholesterol (mmol/l)	4.4 (1.3)	4.6 (0.7)	5.15 (1.3)	5.4 (1.2)
HDL cholesterol (mmol/l)	1.2 (0.4)	1.2 (0.3)	1.2 (0.44)	1.24 (0.42)
LDL cholesterol (mmol/l)	2.5 (1.03)	2.7 (0.8)	3.1 (1.1)	3.3 (1.0)
Serum triglycerides (mmol/l)	1.5 (1.3)	1.6 (1.7)	1.5 (0.9)	1.4 (1.3)
Serum creatinine (mmol/l)	48.3 (14)	51 (14)	74 (25)	79.4 (30)
Creatinine clearance (ml/min)	129 (46.4–482)	138 (74.7–206.9)	106 (39.6–273.4)	96.5 (49.6–178.5)
Albumin excretion rate (µg/min)	5.8 (0.7–290)	4.98 (1.44–91)	4.96 (1.3–2000)	4.85 (2.3–2000)
Proportion with albuminuria, *n* (%)	9 (82)	2 (18)	17 (65.4)	9 (34.6)
HbA_{1c} (%)	14 (6.3– > 14)	13.8 (8.6– > 14)	9.9 (4.4– > 14)	8.0 (5.4– > 14)
Other ECG findings				
IVC defects, *n* (%)	7 (87.5)	1 (12.5)	31 (81.6)	7 (18.4)
ST abnormalities, *n* (%)	8 (61.5)	5 (38.5)	13 (72.2)	5 (27.8)
T-wave inversion, *n* (%)	24 (80)	6 (20)	19 (76.3)	9 (23.7)

Data expressed as median (min–max) and mean (SD) as appropriate. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

ECG-LVH increased by 15% per 10 mmHg higher systolic BP [OR 1.541 (95% CI, 1.089–2.185), $p < 0.01$] (Table 3). The prevalence of ECG-LVH was also higher in hypertensive patients with albuminuria compared to hypertensive patients without albuminuria.

The same model was used separately in type 1 diabetic patients. As described earlier, all type 1 patients with ECG-LVH were diagnosed by the Sokolow-Lyon criterion. Using the same model in these patients did not identify any significant covariate of ECG-LVH.

In type 2 patients, 12 had ECG-LVH diagnosed by the Cornell voltage-duration and 15 by the Sokolow-Lyon criteria. Applying the same univariate logistic regression model on these two groups of patients separately, it identified female gender, higher age, increasing waist circumference, higher systolic and diastolic BP and presence of hypertension or albuminuria as covariates of ECG-LVH by the Cornell voltage-duration criterion (all $p < 0.05$). In a multivariate analysis, systolic BP/10 mmHg was identified as the strongest independent covariate, [OR 2.210 (95% CI, 1.395–3.504), p 5 0.001], followed by female gender [OR 10.475 (95% CI, 1.272–86.274), p 5 0.029]. In a similar model with ECG-LVH by the Sokolow-Lyon criterion as the dependent variable, albuminuria was the only significant covariate of ECG-LVH in both univariate and multivariate logistic regression analyses [OR 1.001 (95% CI, 1.000–1.002), $p < 0.05$].

Clustering of the cardiovascular risk factors differed significantly between type 1 and type 2 diabetics. On average, type 1 patients had 0.8 (range 0–3) additional CV risk factor, while type 2 patients on average had 2.2 (range 0–6). In type 1 diabetics, dyslipidaemia in 30 (30.4%) and albuminuria in 11 (12.4%) patients were the most common additional CV risk factors. In type 2 patients, presence of hypertension was the most common additional CV risk factor present in 78 (54.2%) patients, followed by abdominal obesity, dyslipidaemia, albuminuria and advanced age (Fig. 1). In type 1 patients, 15% of these had one additional CV risk factor and 4.2% had two. Type 2 patients had up to six additional CV risk factors, 14.4% having one, 14% having two and 14.4% having three additional CV risk factors.

Relation of other ECG findings with CV risk factors

In the overall study population, the prevalence of intraventricular conductance abnormalities was significantly higher in type 2 diabetics compared to type 1 patients (26 vs 9%, $p < 0.001$) (Table 1). The prevalence of T-wave inversion and ST-segment abnormality did not differ significantly between type 1 and type 2 patients (Table 1) and was significantly more common in patients with ECG-LVH by either criterion (Table 2).

The associations between prevalence of intraventricular conductance defects and other CV risk factors were assessed in a logistic regression model, including gender, diabetes type, age, diabetes duration, waist circumference, serum cholesterol, serum creatinine, systolic BP, diastolic BP, ECG-LVH, albuminuria and QRS duration among the covariates. In the univariate model, the presence of intraventricular conductance defects was associated with older age, longer duration of diabetes, higher systolic and diastolic BP and longer QRS duration (Table 4). In multivariate analysis, higher systolic BP was the only independent covariate of intraventricular conductance defects.

In a similar model assessing covariates of ST-segment abnormality, female gender [OR 0.43 (95% CI, 0.2–0.9), p 5 0.034], patients with ECG-LVH [OR 3.623 (95% CI, 1.456–9.015), p 5 0.006] and diastolic BP/5 mmHg [OR 1.189 (95% CI, 1.012–1.397), p 5 0.035]

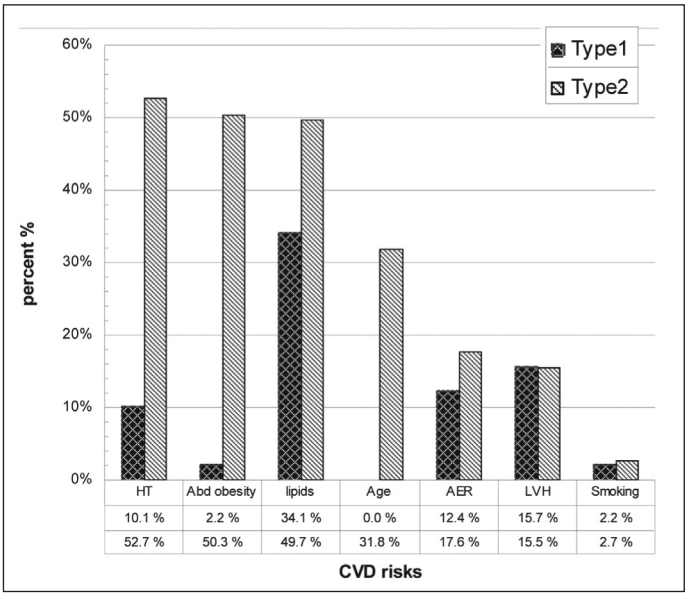

Figure 1. Clustering of cardiovascular risk factors for type 1 and 2 diabetics.

Table 3. Covariates of LVH by either criteria in type 2 diabetic patients indentified by logistic regression analysis

	LVH by any criteria		
Covariates	**Number with LVH (%)**	**Unadjusted (simple) OR (95% CI)**	**Adjusted (multivariate) OR (95% CI)**
Gender: male	10 (15.4)	1.0	
female	13 (15.7)	1.021 (0.417–2.504)	
Age at inclusion (years)	23 (15.6)	1.016 (0.978–1.056)	
Diabetes duration (years)	23 (15.5)	0.968 (0.884–1.060)	
Waist circumference (cm)	22 (15.4)	0.990 (0.955–1.026)	
Serum cholesterol (mmol/l)	23 (15.6)	1.131 (0.808–1.584)	
Serum creatinine (mmol/l)	23 (15.6)	1.007 (0.992–1.023)	
Systolic BP/10 mmHg	22 (15.3) 1.534	(1.081–2.176)**	1.541 (1.089–2.185)**
Diastolic BP/5 mmHg	22 (15.3)	1.131 (0.932–1.373)	
Hypertension: no	9 (12.5)	1.0	
Hypertension: yes	13 (18.1)	1.542 (0.614–3.874)	
Normal AER	14 (11.6)	1.0	
Abnormal AER	9 (34.6)	4.046 (1.517–10.796)**	

Independent covariates involved in the logistic multivariate regression analysis are SBP/10 mmHg and AER. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 4. Covariates of intraventricular conduction defects (IVC) in diabetic patients indentified by logistic regression analysis in the total study population

Covariates	IVC yes n (%)	Unadjusted (univariate) OR (95% CI)	Adjusted (multivariate) OR (95% CI)
Gender: male	23 (50)	1.0	
female	23 (50)	0.835 (0.438–1.591)	
Diabetes type 1	8 (9)	1.00	
Diabetes type 2	38 (25.7)	3.498 (1.549–7.899)**	
Age (years)	46 (19.6)	1.029 (1.011–1.049)**	
Diabetes duration (years)	46 (19.6)	1.070 (1.008–1.136)*	
BMI (kg/m^2)	42 (18.6)	1.067 (1.009–1.129)*	
Serum cholesterol (mmol/l)	46 (20.1)	1.026 (0.869–1.216)	
Serum creatinine (mmol/l)	46 (20.1)	1.007 (0.995–1.018)	
SBP/10 mmHg	44 (20)	1.219 (1.077–1.378)**	1.221 (1.080–1.382)***
DBP/5 mmHg	44 (20)	1.180 (1.046–1.330)**	
LVH: no	38 (19)	1.0	
LVH: yes	8 (21.6)	1.176 (0.498–2.776)	
Normal AER	36 (78.3)	1.0	
High AER	10 (21.7)	1.636 (0.727–3.680)	
QRS duration/40 msec	46 (19.6)	3.526 (1.157–10.743)*	

Independent covariates involved in the multivariate analysis are diabetes type, diabetes duration, age, WC, SBP/10 mmHg and QRS/40 msec.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

were identified as independent covariates of having ST-segment abnormality in a multivariate analysis. When T-wave inversion was the dependent variable in a similar model, the presence of ECG-LVH [OR 1.89 (95% CI, 0.9–3.9), $p < 0.05$) and age [OR 0.98 (95% CI, 0.969–1.000), $p < 0.05$) were associated with the presence of T-wave inversion in a univariate regression analysis.

Discussion

This cross-sectional study was the first to investigate the prevalence and covariates of ECG-LVH in a group of diabetic patients in Dar es Salaam, Tanzania. The main findings from this study were a prevalence of 15.6% of subjects having ECG-LVH among the African diabetic patients, with median diabetes duration of three years; and secondly, identifying systolic BP and albuminuria as the main covariates associated with the presence of ECG-LVH in this study.

The prevalence of ECG-LVH among diabetic patients in sub-Saharan Africa is largely unknown; therefore the present study adds to previous knowledge. Most previous reports on the prevalence of ECG-LVH in Africans come from West Africa, where prevalence ranged from 4.2% using the Cornell voltage criterion among civil workers in Benin,[11] to 22 and 48% using Cornell voltage and Sokolow-Lyon voltage criteria, respectively among hypertensive patients in Nigeria.[12] A study from Kenya in newly diagnosed mild to moderate hypertensive patients found the prevalence of ECG-LVH to be 31.7%.[27] Studies among African-American patients also showed high rates of ECG-LVH in hypertensives, 36.2% by Sokolow-Lyon and 23.4% by Cornell product criteria.[28] The previous finding that more hypertensive African patients with ECG-LVH were picked by Sokolow-Lyon voltage than by Cornell product criteria is in accordance with findings in the present study.

Compared to results from the Eurodiab IDDM Complications study, the prevalence of ECG-LVH in type 1 diabetic patients in the present study was unexpectedly high.[29] It is well known that the Sokolow-Lyon voltage criterion may overestimate the diagnosis of LVH in young, tall or thin subjects as included among the type 1 diabetic patients in our study. However, epidemiological studies in general East-African populations in the Republic of Seychelles reported ECG-LVH by the Sokolow-Lyon voltage criterion in 9.3% of patients.[30] This study also found that the Sokolow-Lyon voltage criterion had low specificity for anatomical LVH in East African populations, suggesting that some race-specific ECG features may interfere with components of ECG-LVH diagnoses by the Sokolow-Lyon voltage criterion.

It is well known that CV risk-factor clustering in diabetic patients is associated with an increased risk for developing renal impairment and coronary vascular complications.[31] In particular, patients with three or more risk factors are more likely to develop CV complications, such as coronary heart disease and stroke.[31] Our finding that the prevalence of two or more cardiovascular risk factors was higher in type 2 than in type 1 diabetic patients (68.3 vs 15.7%, $p < 0.001$) is in accordance with previous findings, and underscores the necessity of broad screening for CV risk factors in type 2 diabetic patients at the time of diagnosis.[32] In multivariate logistic regression, systolic BP and albuminuria were identified as the most important covariates of ECG-LVH.

In the current study, 16 (44.4%) of the patients with ECG-LVH were also hypertensive. ECG-LVH among type 2 diabetics was associated with higher systolic and mean BP as well as the presence of hypertension, and all were significant covariates of the presence of LVH by the Cornell product criterion. However, with multivariate analysis, systolic BP [OR 1.015 (95% CI, 1.001–1.028), $p < 0.05$)] was the only independent covariate of ECG-LVH, while no independent association was found between diastolic BP and ECG-LVH. Similar findings have previously been reported from the LIFE study that included hypertensive patients with ECG-LVH by Cornell product or Sokolow-Lyon criteria.[33] Likewise, in the Framingham study, patients with systolic BP > 180 mmHg had a 50% chance of developing ECG-LVH over 12 years, while no risk association was found with diastolic BP.[7]

Our finding, that hypertension and albuminuria were the main covariates of ECG-LVH is in accordance with previous reports in hypertensive patients and type 2 diabetics.[34,35] Furthermore, Mbanya *et al*. demonstrated a significant correlation between left ventricular hypertrophy by echocardiogram and urinary albumin excretion rate among diabetic patients in Cameroun.[36]

In the current study, the prevalence of ECG-LVH was higher in type 2 diabetic patients with albuminuria than in normalbuminuric patients. Furthermore, the prevalence of ECG-LVH was also higher in hypertensive patients with albuminuria compared to hypertensive patients without albuminuria. The present study adds to previous knowledge by demonstrating a relationship between LVH, hypertension and albuminuria after a short duration of diabetes in Tanzanian type 2 diabetes patients. In the LIFE study, ECG-LVH using Cornell product or by Sokolow-Lyon criteria was associated with a 1.6-fold increase in the prevalence of microalbuminuria and a 2.6-fold increase in the prevalence of macroalbuminuria compared to those without LVH.[10]

In our study, ST-segment depression and T-wave inversion on ECG were associated with having ECG-LVH. The finding is in accordance with previous reports in hypertensive patients, finding strain patterns in the absence of coronary disease to indicate the presence of anatomical LVH.[37,38] But such ECG findings can also indicate myocardial injury.[7,37] However, in the present study population, there were no patients reporting clinical symptoms suggestive of coronary heart disease.

The median HbA_{1c} levels were high in both types of diabetics, indicating poor metabolic control. However, there was no correlation between HbA_{1c} and LVH in this study. Use of the Cornell product and Sokolow Lyon voltage criteria to diagnose ECGLVH has been validated in large studies. However, the accuracy of the criteria used for detecting LVH has been found to vary with body size and gender. For instance, obesity decreased the sensitivity of the Sokolow-Lyon voltage ECG criterion[38] and it was more sensitive in men, while the Cornell product criterion had greater sensitivity with women.[33]

Therefore, in the current population, these ECG criteria only partially identified different diabetic patients. Our findings are in agreements with previous reports from the LIFE study[33] in which the above ECG criteria set for LVH also identified different hypertensive patients with different baseline characteristics. This finding further emphasises the importance of using more than a single criterion to more correctly diagnose patients with ECG-LVH.

Study limitation

The major limitation of this study was that echocardiography was not performed to confirm anatomical LVH in patients with ECG-LVH. We chose ECG for diagnosing LVH because it is a more widely available, cheaper and more easily performed technique, albeit less sensitive and specific than echocardiography, for detection of LVH, in particular within African populations and in young or thin type 1 diabetic patients. However, previous publications from the LIFE study have documented that the majority of patients with ECG-LVH with the criteria used in our study indeed also had LVH detected by echocardiography.[33] As the present study did not include a non-diabetic comparative group, the impact of diabetes alone on prevalence of ECG-LVH in the Tanzanian population could not be determined.

Conclusion

This study demonstrates that ECG-LVH was present in 15.7% of type 1 and 15.5% of type 2 diabetic Tanzanian patients. Systolic BP and albuminuria were identified as the main predictors of the presence of ECG-LVH. Our study also demonstrated that CV risk factors cluster in type 2 diabetics, underscoring the need for broad screening of CV risk factors in these patients to optimise prevention of CV risk complications.

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Blood pressure response to an exercise treadmill test, and echocardiographic left ventricular geometry in Nigerian normotensive diabetics

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Summary

Objectives: **This study evaluated normotensive diabetic patients' blood pressure response to graded exercise and their echocardiographic pattern of left ventricular geometry.**

Methods: **A descriptive, cross-sectional, hospital-based study was carried out on 30 normotensive type 2 diabetic patients and 34 controls, aged 30 to 60 years. The outcome measures were to determine the exercise-related variable, blood pressure response, and left ventricular geometry by means of echocardiography.**

Results: **Nineteen (29.7%) and 11 (17.2%) normotensive diabetic subjects had normal left ventricular geometry and concentric left ventricular remodelling, respectively. None of the subjects had concentric or eccentric left ventricular hypertrophy. On this basis, the normotensive diabetic subjects were divided to two groups: G1 (normal) and G2 (concentric left ventricular remodelling). The groups had comparable mean age, body mass index (BMI), fasting blood glucose (FBG) and two-hour post-prandial blood glucose values, and heart rate, systolic (SBP) and diastolic blood pressure (DBP) at rest. G2 patients had higher mean duration of diabetes than G1 subjects (69.0 ± 9.48 vs 18.7 ± 8.7 months; $p = 0.007$). Peak systolic blood pressure was significantly higher in G2 than G1 subjects (213.6 ± 20.1 vs 200.0 ± 15.3 mmHg; $p = 0.04$). Although there was no statistically significant difference in the left ventricular (LV) mass index between the groups, G2 patients had significantly higher relative wall thicknesses than G1 patients (0.53 ± 0.03 vs 0.41 ± 0.04; $p < 0.001$).**

Conclusion: **Normotensive diabetic subjects with concentric left ventricular remodelling have increased blood pressure reactivity to exercise. It is probable, as suggested in earlier studies, that increased blood pressure reactivity to exercise is an indicator of target-organ damage, particularly in normotensive diabetics.**

Keywords: diabetes, exercise, blood pressure response, left ventricular geometry

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Stress increases blood pressure, and variable individual blood pressure responses have been evaluated with regard to prediction of new-onset hypertension, target-organ damage and incident cardiovascular disease or death.[1] The significance of blood pressure reactivity to exercise has been evaluated, with variable results, in studies on the association between the blood pressure response to exercise and either left ventricular mass or left ventricular geometry in hypertensive patients.[2,3] The exaggerated exercise blood pressure (BP) values in these hypertensive adults have been attributed to impaired endothelial vasodilator function.[4]

Arterial stiffness is also related to type 2 diabetes,[5] mainly due to an impaired endothelial vasodilator function, which in turn is associated with increased afterload,[5] leading to an elevated systolic blood pressure (SBP).[6] These processes consequently lead to structural alterations in the diabetic heart. In normotensive diabetic patients, early and asymptomatic functional and structural abnormalities may alter the normal response to exercise, as already observed in elderly[7] and non-diabetic hypertensive patients.[3] However, not much is known about the relationship between blood pressure response to exercise and sub-clinical cardiac end-organ damage in normotensive diabetics, particularly in Nigeria.

In light of the above, we set out to investigate the relationship between blood pressure response to graded exercise in normotensive diabetics and their echocardiographic pattern of left ventricular geometry, as evidence of cardiac end-organ damage.

Methods

Thirty normotensive type 2 diabetic subjects (male = 15; female = 15) and 34 normal controls (male = 17; female = 17) aged 30 to 60 years were recruited through the medical out-patient department

of Obafemi Awolowo University Teaching Hospitals complex (OAUTHC), Ile Ife, Nigeria. Ethical clearance for the study was approved by the Ethics and Research Committee of the Hospital in conformity with ethical guidelines of the 1975 Declaration of Helsinki, and all participants gave written consent to participate.

Demographic parameters of the subjects were noted and recorded. All subjects were clinically examined to evaluate their body mass index (BMI) and cardiovascular status at rest. Subjects were considered diabetic if they had fasting plasma glucose (FBG) values ≥ 126 mg/dl (7.0 mmol/l)[8] or if they used hypoglycaemia medication. Fasting plasma glucose and two-hour post-prandial plasma glucose (2HPP) values were obtained 24 hours prior to the procedures.

A resting 12-lead ECG was done to exclude patients with baseline ST-segment abnormalities and bundle branch block. Also excluded were patients with coexisting hypertension or who were on antihypertensive(s), those with established chronic renal failure or serum creatinine levels > 1.5 mg% (132 µmol/l), congestive heart failure, valvular heart disease and other diseases known to influence LV function, such as thyroid disease and severe obesity.

All the subjects underwent treadmill-symptom limited maximal exercise using the Bruce protocol.[9] The protocol continued until one of several endpoints was reached. These included if the patient achieved the age-predicted maximum heart rate; requested that the exercise be terminated; developed severe chest pain, fatigue, leg discomfort or dyspnea; developed frequent premature ventricular beats; developed a systolic blood pressure > 250 mmHg or a drop in the pre-test systolic blood pressure > 10 mmHg; or developed any other problems necessitating termination of exercise.

The subjects also had transthoracic two-dimensional (2D) and 2D derived M-mode echocardiography performed, according to standard procedure,[10] with simultaneous electrocardiographic recordings while in the left lateral decubitus position, using a standard ultrasound machine (Sonoline G60S Ultrasound Imaging System) with 4.2-MHz transducer. Left ventricular enddiastolic measurements were taken during at least three cycles[11] and included left ventricular internal diameter (LVIDD), posterior wall thickness (PWT) and interventricular septal thickness (IVST). Left ventricular mass was estimated from the American Society of Echocardiography's formula[11]:

Estimated LV mass index (g/m^2) = 0.80 [1.04 (LVIDD + PWT + IVST)3 – (LVIDD)3] + 0.6 g/BSA

Upper normal limits for LV mass index were 134 and 110 g/m^2 in men and women, respectively.[12] Relative wall thickness (2 × posterior wall thickness/LV diastolic diameter) was calculated.[13] A partition value of 0.45 for relative wall thickness was used for both men and women.[14] Patients with increased LV mass index and increased relative wall thickness were considered to have concentric hypertrophy, and those with increased LV mass index and normal relative wall thickness were considered to have eccentric hypertrophy. Those with normal LV mass index and increased or normal relative wall thickness were considered to have concentric remodelling or normal geometry, respectively.

Results

The diabetic subjects and controls had comparable ages and BMIs (48.37 ± 6.96 vs 48.35 ± 6.13 years; $p = 0.197$ and 24.82 ± 3.66 vs 24.38 ± 1.94 kg/m^2; $p = 0.861$, respectively). Diabetic subjects had significantly higher FBG values than the controls (8.94 ± 2.13 vs 4.75 ± 0.37 mmol/l; $p \leq 0.001$).

As shown in Table 1, normotensive diabetic subjects had higher exercise-induced haemodynamic parameters of peak systolic (pSBP) and peak diastolic blood pressure (pDBP) but lower peak heart rates (pHR). There was no statistically significant difference in left ventricular mass index (LVMI). Nineteen (29.7%) and 11 (17.2%) normotensive diabetic subjects had normal left ventricular geometry and concentric left ventricular remodelling, respectively. None of the normotensive diabetic subjects had concentric or eccentric left ventricular hypertrophy. Thirty (46.8%) and four (6.3%) controls had normal left ventricular geometry and concentric left ventricular remodelling, respectively. None of the subjects had concentric or eccentric left ventricular hypertrophy.

The normotensive diabetic subjects were then divided into two groups: G1 (normal) and G2 (concentric left ventricular remodelling) on this basis. The groups had comparable mean ages, BMIs, FBG and two-hour post-prandial blood glucose values, heart rates, and SBP and DBP at rest (Table 2). G2 patients had a higher mean duration of diabetes than G1 (69.0 ± 9.48 vs 18.7 ± 8.7 months; p

Table 1. Haemodynamic response and echocardiographic pattern of the study population

Parameters	Normotensive diabetics (n = 30))	Controls (n = 34)	p-value (Student's t-test)
rHR (per min)	91.37 ± 16.10	83.29 ± 5.36	0.038
rDBP (mmHg)	73.03 ± 5.46	71.94 ± 3.13	0.713
rSBP (mmHg)	117.13 ± 6.36	113.62 ± 4.51	0.044
pHR (per min)	166.00 ± 15.61	179.03 ± 9.10	< 0.001
pDBP (mmHg)	95.67 ± 9.35	89.12 ± 7.12	< 0.001
pSBP (mmHg)	205.00 ± 18.15	185.41 ± 10.81	< 0.001
Exercise capacity (METs)	8.07 ± 1.47	8.11 ± 0.88	0.992
LVMI (g/m^2)	93.97 ± 17.04	90.55 ± 17.09	0.512
IVST (mm)	10.24 ± 1.36	9.45 ± 1.44	0.084
PWT (mm)	9.70 ± 1.51	9.43 ± 1.50	0.771
RWT	0.45 ± 0.68	0.41 ± 0.07	0.038

Statistical significance at $p < 0.05$;
Values are expressed as mean ± SD;
rHR = resting heart rate, pHR = peak heart rate.

Table 2. Clinical and demographic pattern of G1 and G2 subjects

Parameters	Normal LV geometry (n = 19)	Concentric LV remodelling (n = 11)	p-value (Student's t-test)
Age	48.68 ± 7.7	47.82 ± 5.7	0.749
Gender			
M: n (%))	7 (36.8%)	8 (72.7%)	0.058*
F: n (%)	12 (63.2%)	3 (27.3%)	
BMI (kg/m^2)	24.8 ± 4.1	24.8 ± 2.9	0.992
Duration of diabetes (months)	18.7 ± 8.7	69.0 ± 9.48	0.007
FBG (mmol/l)	9.8 ± 2.03	8.1 ± 1.9	0.082
2HPP (mmol/l)	12.2 ± 1.9	13.8 ± 3.5	0.236
rHR (bpm)	92.1 ± 18.2	90.1 ± 12.4	0.748
rDBP (mmHg)	72.4 ± 5.8	74.2 ± 4.9	0.390
rSBP (mmHg)	118.5 ± 6.5	114.7 ± 5.6	0.116
rPP (mmHg)	46.2 ± 8.7	40.6 ± 3.9	0.052

Statistical significance at p < 0.05;
*Chi-square. Values are expressed as mean ± SD

Table 3. Exercise-induced haemodynamic factors

Parameters	Normal LV geometry (n = 19)	Concentric LV remodelling (n = 11)	p-value (Student's t-test)
pHR (bpm)	167.8 ± 10.9	162.8 ± 21.7	0.405
pDBP (mmHg)	94.2 ± 7.7	98.2 ± 11.7	0.270
pSBP (mmHg)	200.0 ± 15.3	213.6 ± 20.1	0.045
ΔHR (bpm)	75.7 ± 18.4	72.7 ± 28.1	0.725
ΔDBP (mmHg)	21.5 ± 14.1	24.0 ± 13.3	0.596
ΔSBP (mmHg)	81.5 ± 14.1	98.9 ± 20.1	0.010
ΔPP (mmHg)	105.8 ± 9.6	115.5 ± 11.3	0.019
HR reserve	0.97 ± 0.16	0.87 ± 0.03	0.222
Exercise capacity (METs)	8.5 ± 1.5	7.4 ± 1.1	0.042

Statistical significance at p < 0.05
Values are expressed as mean ± SD.

= 0.007). The patients' characteristics at rest were not statistically significantly different (Table 2).

As shown in Table 3, peak systolic blood pressure was significantly higher in G2 subjects than in G1 (213.6 ± 20.1 vs 200.0 ± 15.3 mmHg; p = 0.04). The difference between resting systolic and peak systolic blood pressure (ΔSBP) as well as resting pulse pressure and pulse pressure during exercise (ΔPP) followed a similar trend to that of peak systolic blood pressure. Exercise capacity in G2 subjects was significantly lower than in G1 by 12.94% (7.4 ± 1.1 vs 8.5 ± 1.5 METs; p = 0.042). Although, there was no statistically significant difference between the LV mass index in the two groups, G2 subjects had significantly higher relative wall thicknesses than those in G1 (0.53 ± 0.03 vs 0.41 ± 0.04; p < 0.001) (Table 4).

Table 4. Echocardiographic parameters of G1 and G2 subjects

Parameters	Normal LV geometry (n = 19)	Concentric LV remodelling (n = 11)	p-value (Student's t-test)
LVMI (g/m²)	81.1 ± 13.4	88.9 ± 21.8	0.233
IVST (mm)	9.8 ± 1.2	11.1 ± 1.3	0.010
PWT (mm)	9.0 ± 1.3	10.9 ± 1.1	< 0.001
RWT	0.41 ± 0.04	0.53 ± 0.03	< 0.001

Statistical significance at p < 0.05
Values are expressed as mean ± SD.

Discussion

The relationship of blood pressure response to exercise and endorgan damage in hypertensive subjects is not clear. Studies on this subject in diabetics are few, especially among blacks, who unfortunately are at higher risk of developing cardiovascularrelated complications than their Caucasian counterparts.[15] This study is the first in Nigeria to assess the relationship between blood pressure response to exercise and abnormal LV geometry.

In this study, gender, age and BMI were comparable among the patients with normal LV geometry and those with LV concentric remodelling. The longer duration of diabetes in patients with concentric LV remodelling supports the earlier assertion that the longer the duration of diabetes, the more the likelihood that the patient will develop cardiovascular complications. This was despite the fact that short-term (FBG, two-hour post-prandial blood glucose) glycaemic control was similar in both groups in this study, suggesting that blood pressure response during exercise may not have been much influenced by blood glucose exposure.

It has been suggested that blood pressure response may be related to blood glucose control.[16] Marfella *et al*. reported that in the resting state, the presence of hyperglycaemia led to an increase in SBP and DBP independently of endogenous insulin in 20 patients with type 2 diabetes. A reduced availability of nitric oxide was suggested as a possible explanation.[16] In our study, the peak systolic blood pressure during exercise was significantly higher in patients with LV concentric remodelling than in those with normal LV geometry. This however was not the case with peak diastolic blood pressure. This was reflected in the significant change in pulse pressure (ΔPP) observed during exercise. Pulse pressure provides a crude guide to stiffness of the large conduit arteries.[17] Physiological parameters related to blood pressure regulation and potential contributors to reduced exercise capacity in type 2 diabetic individuals include reduced LV systolic volume, altered myocardial and diastolic functions and increased arterial stiffness.[5,18] The elevated peak exercise SBP observed in patients with concentric left ventricular remodelling in this study was probably partly associated with arterial stiffness, as reflected by the higher ΔPP.[5,6]

Exercise capacity was also reduced in patients with LV concentric hypertrophy in our study. This may provide additional explanation for reduced exercise tolerance in normotensive diabetes patients. It has been suggested that the voltage on the ECG of left ventricular hypertrophy may be an early marker of impaired exercise capacity.[19] Previous studies have shown that left ventricular hypertrophy independently predicted reduced exercise capacity.[20] This study has shown that type 2 diabetic patients with increased peak systolic blood pressure had increased arterial stiffness, higher LVMI, abnormal LV geometry and reduced exercise capacity.

Conclusion

Normotensive diabetics with concentric left ventricular remodelling have increased systolic blood pressure reactivity to exercise. It is probable, as suggested in earlier studies, that increased blood pressure reactivity to exercise is an indicator of target-organ damage, especially in normotensive diabetics.

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Encapsulated beta-cell replacement therapy for type 1 diabetes

Beta-cell encapsulation therapy is a procedure that involves implantation of cells, contained in a protective barrier, with the ability to secrete insulin into the body in a glucose-responsive manner.

On 17 July 2014, the Juvenile Diabetes Research Foundation (JDRF) announced that its partner, ViaCyte, Inc, had filed an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA), seeking to conduct a phase 1 and 2 clinical trial in patients with type 1 diabetes. The purpose of this trial is to evaluate the safety and efficacy of the VC-01 product, a stem cell-derived, encapsulated-cell replacement therapy. In addition to the IND, ViaCyte also submitted a medical device master file (MAF) to the FDA regarding the Encaptra® drug-delivery system, a device component of the VC-01 product.

Beta-cell encapsulation therapy is a procedure that involves implantation in a protective barrier of cells with the ability to secrete insulin into the body in a glucose-responsive manner. The advantage of these encapsulated beta-cells is that they can assess the patient's blood glucose level and secrete the correct amount of insulin, while their barrier protects them from being destroyed by the autoimmune system. More importantly, encapsulation therapy also helps prevent the requirement of lifetime administration of powerful and toxic immunosuppressive drugs designed to protect the newly introduced islets from the immune system.

VC-01 therapy is the combination of PEC-01 cells (a proprietary pancreatic endoderm cell product derived through directed differentiation of an inexhaustible human embryonic stem cell) and an Encaptra drug-delivery system (a proprietary immune-protecting and retrievable encapsulation medical device.) The VC-01 combination product is expected to be implanted under the skin of the patient through a simple out-patient surgical procedure. Once inside the body, the cells are expected to differentiate and become mature pancreatic cells with the ability to produce and secrete insulin based on the patient's glucose level.

Based on pre-clinical studies, VC-01 therapy has been shown to be effective in mice. Normal blood glucose levels for mice range from 160–200 mg/dl (8.88–11.1 mmol/l) , which are considered hyperglycaemic in humans. However, when the mice received the VC-01 combination product, their blood glucose levels were closer to human levels. In addition, when these mice received STZ, a chemical designed to kill native mouse beta-cells, the mice still maintained their blood glucose levels.

Study of the synergy of cell therapy and the Encaptra medical device also showed positive results. In the mouse study, host blood vessels began to grow into the VC-01 combination product at week four, supplying a steady amount of oxygen and nutrients to PEC-01 cells. At week eight, vascularisation developed quickly. Meanwhile, the Encaptra device protected the PEC-01 cells from immune rejection with a protective permeable membrane.

The VC-01 cell replacement therapy could be a potential cure for type 1 diabetes.

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Increased relative wall thickness is a marker of subclinical cardiac target-organ damage in African diabetic patients

PILLY CHILLO, JOHNSON LWAKATARE, JANET LUTALE, EVA GERDTS

Abstract

Objective: **To assess the prevalence and covariates of abnormal left ventricular (LV) geometry in diabetic outpatients attending Muhimbili National Hospital in Dar es Salaam, Tanzania.**

Methods: **Echocardiography was performed in 61 type 1 and 123 type 2 diabetes patients. LV hypertrophy was taken as LV mass/height$^{2.7}$ > 49.2 g/m$^{2.7}$ in men and > 46.7 g/m$^{2.7}$ in women. Relative wall thickness (RWT) was calculated as the ratio of LV posterior wall thickness to end-diastolic radius and considered increased if ≥ 0.43. LV geometry was defined from LV mass index and RWT in combination.**

Results: **The most common abnormal LV geometries were concentric remodelling in type 1 (30%) and concentric hypertrophy in type 2 (36.7%) diabetes patients. Overall, increased RWT was present in 58% of the patients. In multivariate analyses, higher RWT was independently associated with hypertension, longer isovolumic relaxation time, lower stress-corrected midwall shortening and circumferential endsystolic stress, both in type 1 (multiple R^2 = 0.73) and type 2 diabetes patients (multiple R^2 = 0.66), both p < 0.001. These associations were independent of gender, LV hypertrophy or renal dysfunction.**

Conclusion: **Increased RWT is common among diabetic sub-Saharan Africans and is associated with hypertension and LV dysfunction.**

Keywords: left ventricular geometry, African diabetes, relative wall thickness

The co-existence of diabetes with other cardiovascular risk factors, such as hypertension and obesity, may contribute to the association of diabetes with subclinical cardiac targetorgan damage such as left ventricular (LV) hypertrophy and dysfunction. In addition, several reports have suggested that diabetes has direct adverse effects on the heart, independent of obstructive coronary artery disease.[1,2] In the Strong Heart study, non-insulin dependent diabetes was associated with a 12 to 14% higher LV mass/height$^{2.7}$ as well as reduced LV systolic functio and increased arterial stiffness.[3] Among hypertensive diabetic African Americans, increased relative wall thickness (RWT) and LV hypertrophy have been found to be more prevalent,[4,5] and earlier development of cardiac end-organ damage than in Caucasians has been suggested.[6]

In sub-Saharan Africa, diabetes and other cardiovascular diseases were considered rare.[7] As a result, research focus has been on infectious diseases. However, recent publications in the region have shown an increase in the prevalence of diabetes, hypertension and other cardiovascular risk factors,[8] and a high prevalence of LV hypertrophy, in particular in hypertensive patients, has been reported.[9] However, there are limited data on subclinical cardiac target-organ damage in diabetic patients.

The aim of the present study was therefore to determine the prevalence and covariates of abnormal LV geometry among type 1 and type 2 diabetes outpatients of African origin attending Muhimbili National Hospital in Dar es Salaam, Tanzania.

Methods

This study was a prospectively planned follow-up examination of 244 diabetic patients of African origin who participated in a diabetes study programme that included clinical and biochemical examination at Muhimbili National Hospital in Dar es Salaam, Tanzania in 2003–2004.[10,11] Of the total 244 patients who participated in the first survey, 184 patients (75%) were still receiving care at the diabetes outpatient clinic in Muhimbili National Hospital in 2008. Patients were informed about the follow-up study when attending their regular visits at the diabetes outpatient clinic and subsequently invited to participate. All 184 patients agreed to participate and signed informed consent.

A structured questionnaire was used for interviewing the patients on socio-demographic characteristics, history of other cardiovascular risk factors and duration of diabetes. Height and weight were measured and used to calculate body mass index. Waist circumference was measured at the level of the umbilicus and used as a measure of central obesity. Blood pressure was measured using a mercury sphygmomanometer and appropriate cuff size. After five minutes' rest in the sitting position, a set of three readings was taken five minutes apart. The average of the last two readings was taken as the patient's clinic blood pressure.[12] Hypertension was defined as blood pressure ≥ 140/90 mmHg or use of antihypertensive medication.

Fasting capillary blood glucose and glycated haemoglobin (HbA_{1c}) levels were measured on spot; blood glucose by a HemoCue AB glucose analyser (Angelholm, Sweden) and HbA_{1c} using a DCA 2000+ analyser (Bayer Inc., New York, USA). Urinary albumin/creatinine ratio (UACR) was measured in a spot morning urine sample using the same DCA 2000+ analyser, which measures urine albumin (in mg/l) and creatinine (in mg/dl) concentrations and calculates the urine albuminto-creatinine ratio (UACR). Microalbuminuria was defined as UACR > 30 mg/g and macroalbuminuria as UACR >

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300 mg/g.[13] Biochemical tests were performed with the use of a chemistry analyser (Abbott Architect, Illinois, USA) at Muhimbili National Hospital laboratory, which is the National reference laboratory.

All patients gave written informed consent. The study was ethically approved by the Muhimbili University of Health and Allied Sciences' research and publication committee.

All echocardiograms were performed by the same licensed cardiologist, who had received special training in echocardiography (PC), using a SONOS 7500 Phillips echocardiogram machine. Patients were examined in the left lateral decubitus position using a 3-MHz transducer. The echocardiographic protocol included parasternal long- and short-axis views of the left ventricle, left atrium and aorta, as well as two-, three- and four-chamber images of the left ventricle and pulsed Doppler recordings of LV filling. Spectral tissue Doppler was recorded of mitral annular plane velocity in the apical four-chamber view.

All images were recorded digitally on Magnetic Optical disks, and interpretation of all digital echocardiograms was done at the Department of Heart Diseases, Haukeland University Hospital using a Tomtec (TomTech Imaging Systems GmbH, Unterschielssheim, Germany) work station for post-processing. All studies were first read by the primary investigator and then proof read by the senior investigator, a highly experienced reader (EG).

Quantitative echocardiography was performed following the American Society of Echocardiography guidelines.14 LV hypertrophy was considered present when LV mass indexed for height$^{2.7}$ exceeded 49.2 g/m$^{2.7}$ in men and 46.7 g/m$^{2.7}$ in women.[15] RWT was calculated as the ratio of end-diastolic posterior wall thickness to end-diastolic LV internal radius and considered increased if ≥ 0.43.

Patients were categorised into four LV geometric patterns based on LV mass/height$^{2.7}$ (LVMI) and RWT measurements in combination. Normal geometry was considered present if LVMI and RWT were both normal, concentric remodelling was the combination of normal LVMI and increased RWT, eccentric hypertrophy was the combination of LV hypertrophy and normal RWT, and concentric LV hypertrophy was present if LV hypertrophy and increased RWT were both present.[14]

LV circumferential end-systolic stress (CESS) was estimated at the midwall using a cylindrical model.[16] Myocardial contractility was assessed by midwall fractional shortening (MWS), calculated using a previously validated formula, taking into consideration the epicardial migration of the midwall during systole.[17] Stress-corrected fractional shortening (scFS) and stress-corrected MWS (scMWS) were calculated as the ratio between actual and predicted FS and MWS for actual CESS, respectively, using previously published equations.[17]

Transmitral flow was recorded with pulsed-wave Doppler between the mitral cusp tips in the apical four-chamber view. The early (E) and atrial (A) waves were traced for peak velocities and used to calculate the E/A ratio. Isovolumic relaxation time was measured from the leading edge of the aortic valve closure spike to the leading edge of the mitral valve high-intensity echo in five-chamber view. Early diastolic mitral annular plane velocity (E') was measured by spectral tissue Doppler in the apical fourchamber view.[18]

Statistical analysis

Data management and statistical analysis was performed using SPSS for Windows version 18.0. Data are presented as mean ± SD for continuous variables and as percentages for categorical variables. Groups of patients were compared using the χ^2 test for categorical variables and unpaired Student's *t*-test, one way ANOVA with Sheffe's *post hoc* test or general linear model with Sidak's *post hoc* test for continuous variables, as appropriate. Bivariate correlations were assessed by Pearson's correlation coefficients. Covariates of increased RWT were identified in the total study population and in groups of type 1 and type 2 diabetes patients by multiple linear regression analyses, run with an enter procedure and co-linearity statistics. A two-tailed *p*-value ≤ 0.05 was considered statistically significant.

Table 1. Demographic and laboratory characteristics of type 1 and type 2 diabetes patients

Characteristic	Type 1 (*n* = 61)	Type 2 (*n* = 123)	*p*-value
Age (years)	21.7 ± 10.6	55.0 ± 9.6	< 0.001
Females, *n* (%)	34 (55)	78 (64)	0.265
Duration of diabetes (years)	8.2 ± 4.5	10.7 ± 6.3	0.005
Body mass index (kg/m^2)	20.9 ± 4.4	28.4 ± 4.7	< 0.001
Obesity, *n* (%)	2 (3.3)	45 (36.6)	< 0.001
Waist circumference (cm)	74 ± 12	98 ± 11	< 0.001
Systolic blood pressure (mmHg)	117 ± 21	147 ± 22	< 0.001
Diastolic blood pressure (mmHg)	74 ± 14	88 ± 11	< 0.001
Hypertension, *n* (%)	11 (17.7)	100 (82.0)	< 0.001
Pulse pressure (mmHg)	43 ± 12	59 ± 17	< 0.001
Fasting blood glucose (mmol/l)	12.2 ± 4.4	10.4 ± 4.7	0.015
HbA_{1c} (%)	10.9 ± 2.2	9.8 ± 2.3	0.003
Total cholesterol (mmol/l)	4.7 ± 1.6	5.6 ± 1.5	0.001
HDL cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.3	0.855
LDL cholesterol (mmol/l)	3.2 ± 1.3	4.0 ± 1.4	< 0.001
Triglycerides (mmol/l)	1.6 ± 1.6	1.7 ± 1.0	0.617
Serum creatinine (µmol/l)	84 ± 70	106 ± 77	0.058
eGFR (ml/min/1.73 m^2)	106 ± 47	81 ± 24	< 0.001
Low eGFR, *n* (%)	6 (10)	21 (18)	0.268
Albuminuria, *n* (%)	24 (40.0)	39 (33.6)	0.412
Microalbuminuria, *n* (%)	16 (26.7)	33 (28.4)	0.860
Macroalbuminuria, *n* (%)	8 (13.3)	6 (5.2)	0.077

HbA_{1c} = glycated haemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, eGFR = estimated glomerular filtration rate.

Results

The study population included 61 type 1 and 123 type 2 diabetes patients. Compared to type 1 patients, type 2 patients were older, had longer duration of diabetes and included more hypertensive and obese patients (all $p < 0.01$) (Table 1).

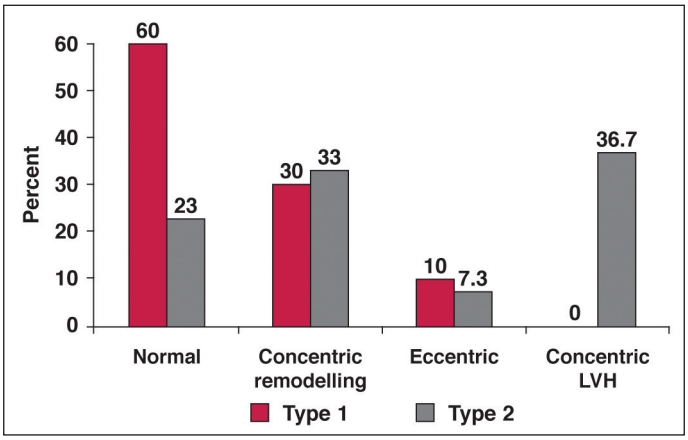

Figure 1. LV geometric patterns in type 1 (red bars) and type 2 (grey bars) diabetes patients. The differences between normal geometry and concentric LVH were statistically significant, both $p < 0.001$.

Table 2. Echocardiographic findings in type 1 and type 2 diabetes patients

	Unadjusted			Adjusted for age and systolic blood pressure		
Echocardiographic finding	**Type 1 (*n* = 61)**	**Type 2 (*n* = 123)**	***p*-value**	**Type 1 (*n* = 61)**	**Type 2 (*n* = 123)**	***p*-value**
Interventricular septum in diastole (cm)	0.91 ± 0.21	1.27 ± 0.31	< 0.001	1.11 ± 0.06	1.16 ± 0.04	0.573
LV posterior wall in diastole (cm)	0.79 ± 0.17	1.06 ± 0.25	< 0.001	0.94 ± (.05	0.98 ± 0.03	0.622
LV end-diastolic diameter (cm)	4.01 ± 0.63	4.21 ± 0.58	0.036	4.10 ± 0.13	4.16 ± 0.08	0.769
Relative wall thickness	0.40 ± 0.10	0.52 ± 0.19	< 0.001	0.48 ± 0.04	0.48 ± 0.02	0.938
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	33.0 ± 9.6	49.2 ± 16.8	< 0.001	40.6 ± 3.0	45.1 ± 1.8	0.299
Fractional shortening (%)	37 ± 5	35 ± 6	0.176	36 ± 1.3	36 ± 0.8	0.940
Stress-corrected fractional shortening (%)	99 ± 11	99 ± 16	0.942	100 ± 3	99 ± 2	0.739
Ejection fraction (%)	65 ± 7	63 ± 8	0.328	63 ± 2	64 ± 1	0.554
Midwall shortening (%)	16 ± 3	13 ± 3	< 0.001	14 ± 0.7	15 ± 0.4	0.875
Stress-corrected midwall shortening (%)	90 ± 17	74 ± 18	< 0.001	80 ± 3.8	81 ± 2.4	0.918
Transmitral E/A ratio	1.5 ± 0.4	0.9 ± 0.3	< 0.001	1.2 ± 0.8	1.1 ± 0.5	0.226
Deceleration time (ms)	165 ± 52	206 ± 61	< 0.001	191 ± 13	192 ± 8	0.954
Isovolumic relaxation time (ms)	62 ± 16	81 ± 20	< 0.001	78 ± 3.8	73 ± 2.4	0.378
Early tissue Doppler velocity (E') (cm/s)	10.3 ± 2.3	6.5 ± 2.4	< 0.001	8.3 ± 0.5	7.5 ± 0.3	0.305
E/E' ratio	9.5 ± 2.4	11.7 ± 4.4	< 0.001	11.2 ± 0.8	10.8 ± 0.5	0.733

Compared to type 1 diabetes patients, type 2 patients had larger LV dimensions and higher RWT and LVMI (Table 2). LV systolic chamber function measured as stress-corrected fractional shortening and ejection fraction did not differ between the two groups, while myocardial contractility assessed by stresscorrected midwall shortening was significantly lower among type 2 diabetes patients (Table 2). Measures of diastolic function were also significantly unfavourable in the type 2 diabetes patients (Table 2). However, LV dimension and function did not differ between the two types of diabetes when adjustment for age and systolic blood pressure was done (Table 2).

In the total population, the prevalence of concentric remodelling, eccentric hypertrophy and concentric hypertrophy was 32, 8.3 and 23.7%, respectively. LV geometry differed significantly between type 1 and type 2 diabetes patients as a consequence of more type 2 diabetes patients having concentric LV hypertrophy (Fig. 1). Systolic blood pressure and body mass index were among the most important covariates of LV geometry in the total study population (Figs 2, 3).

In logistic regression analysis involving the total study population, LV hypertrophy (combined eccentric and concentric LV hypertrophy) was associated with obesity, (OR 3.97, 95% CI: 1.65–9.54, p = 0.002), hypertension (OR 4.58, 95% CI: 1.32–15.85, p = 0.016) and albuminuria (OR 2.31, 95% CI: 1.01–5.27, p = 0.047). This was independent of age, gender, type or duration of diabetes (Table 3).

The most prevalent types of abnormal LV geometry were concentric remodelling in type 1 diabetes patients and concentric LV hypertrophy in type 2 diabetes patients (Fig. 1). Overall, 58% of the total population had increased RWT. In univariate linear regression analysis, the most important correlates of higher RWT were older age, higher blood pressure and higher log UACR, both in type 1 and type 2 diabetes patients (all p < 0.05) (Table 4). In addition, lower eGFR and high-density lipoprotein (HDL) cholesterol were significantly correlated with higher RWT among type 2 but not in type 1 diabetes patients. Having increased RWT was also associated

Table 3. Independent predictors of LV hypertrophy in the total population by logistic regression analysis

Variable	**Odds ratio (95% CI)**	***p*-value**
Obesity	3.97 (1.65–9.54)	0.002
Hypertension	4.58 (1.32–15.85)	0.016
Albuminuria	2.31 (1.01–5.27)	0.047
Age (years)	1.03 (0.98–1.08)	0.206
Male gender	0.66 (0.28–1.53)	0.329
Type of diabetes (type 1 vs type 2)	0.73 (0.13–4.17)	0.727
Duration of diabetes (years)	0.99 (0.92–1.06)	0.785

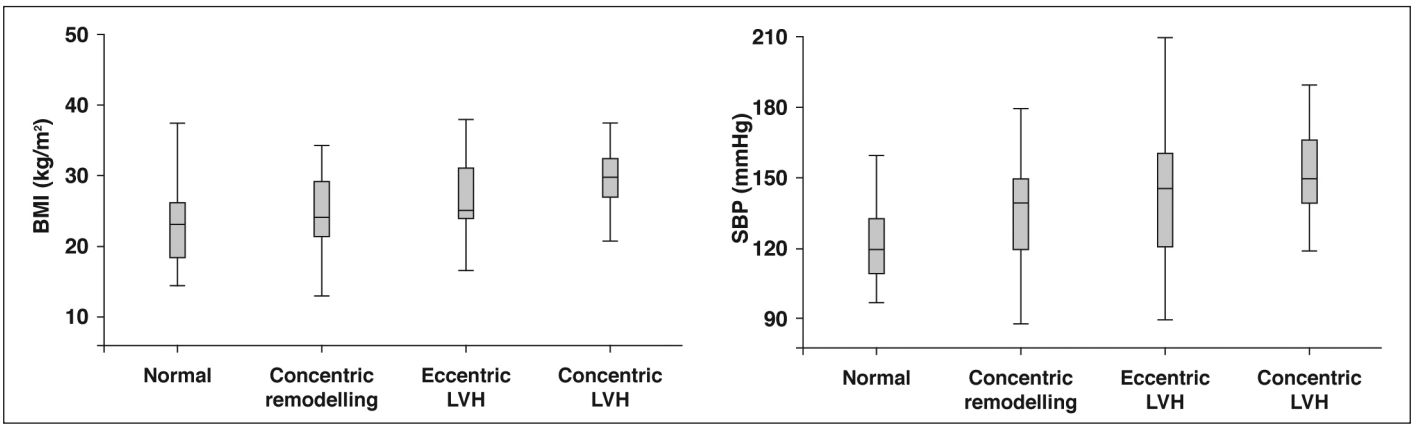

Figure 2. LV geometry in relation to body mass index and systolic blood pressure, and impact on comparison between the different LV geometric patterns; p < 0.001 for comparison of body mass index (left panel) and systolic blood pressure (right panel) in the four geometric patterns by ANOVA.

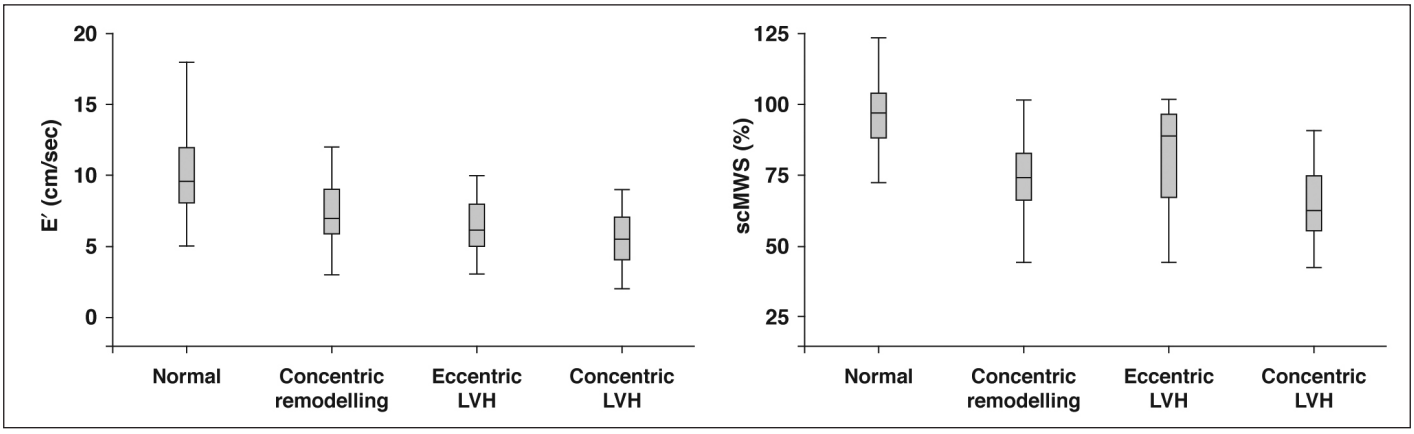

Figure 3. Early tissue Doppler velocity (E') and stress-corrected midwall shortening (scMWS) in relation to LV geometric patterns; $p < 0.001$ for comparison of E' (left panel) and scMWS (right panel) in the four geometric patterns by ANOVA.

with impaired systolic and diastolic LV function, including lower myocardial contractility, measured as scMWS, and delayed early LV diastolic relaxation, measured as longer IVRT, longer deceleration time and reduced E/A ratio, both in type 1 and type 2 diabetes patients (all $p < 0.05$) (Table 4).

When multivariate linear regression analyses were performed, higher systolic blood pressure, longer IVRT and low scMWS remained significant covariates of higher RWT both in type 1 and type 2 diabetes patients, irrespective of presence or absence of LV hypertrophy and also adjusted for CESS. In addition, low eGFR continued to be an independent covariate of higher RWT in type 2 diabetes patients. Substituting log UACR for eGFR in the type 1 diabetes patients' model did not give any independent association either (Table 5).

In binary logistic regression analysis, including type of diabetes, albuminuria, obesity, history of hypertension and HbA_{1c} level, the independent covariates of increased RWT were: type 2 diabetes (OR 2.7, 95% CI: 1.08–7.00), albuminuria (OR 2.2, 95% CI: 1.01–4.62), obesity (OR 2.6, 95% CI: 1.02–6.58) and hypertension (OR 2.5, 95% CI: 1.02–5.87), all $p < 0.05$.

A risk score was calculated based on the beta coefficients in this model: risk score = 9x (type of diabetes) + 8x (albuminuria) + 9x (obesity) + 9x (hypertension). For each parameter included in the score, a value of 1 was assigned if the variable was present or 0 if it was absent. Therefore the individual risk score varied in this study population between 0 and 35 points. Based on the ROC curve analysis, the optimal cut-off point for the prediction of increased RWT was a score of 13 points (area under the curve = 0.77, $p < 0.001$, sensitivity = 76% and specificity = 67%). This risk score had a positive predictive value of 76% (Fig. 4).

Discussion

From echocardiographic studies in Caucasians, North American Indians and African Americans, it is well known that diabetes is associated with concentric LV remodelling, and LV hypertrophy is particularly common in patients with combined type 2 diabetes and hypertension.[19,20] However, few studies have reported on

Table 4. Correlates of RWT in the total population and in type 1 and type 2 diabetes patients

	Total population		Type 1		Type 2	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
Age (years)	0.391	< 0.001	0.357	0.005	0.203	0.035
Body mass index (kg/m^2)	0.237	0.002	0.068	0.605	0.031	0.752
Systolic blood pressure (mmHg)	0.383	< 0.001	0.359	0.004	0.234	0.015
Diastolic blood pressure (mmHg)	0.388	< 0.001	0.331	0.009	0.282	0.003
Fasting blood glucose (mmol/l)	0.029	0.705	0.204	0.118	0.068	0.485
HbA_{1c} (%)	–0.009	0.909	0.113	0.390	0.066	0.496
eGFR (ml/min/1.73 m^2)	–0.282	< 0.001	–0.076	0.563	–0.319	0.001
HDL cholesterol (mmol/l)	–0.165	0.033	–0.146	0.265	–0.277	0.002
Triglycerides (mmol/l)	0.134	0.082	0.279	0.031	0.079	0.416
Triglyceride-to-HDL cholesterol ratio	0.108	0.163	0.141	0.287	0.175	0.069
Log UACR (mg/g)	0.147	0.059	0.259	0.048	0.194	0.045
E' (cm/sec)	–0.434	< 0.001	–0.149	0.246	–0.377	< 0.001
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	0.477	< 0.001	0.113	0.389	0.426	< 0.001
E/A ratio	–0.382	< 0.001	–0.321	0.012	–0.241	0.012
Deceleration time (ms)	0.313	< 0.001	0.255	0.047	0.228	0.017
Isovolumic relaxation time (ms)	0.428	< 0.001	0.304	0.017	0.347	< 0.001
Circumferential end-systolic stress (dyne/cm^2)	–0.421	< 0.001	–0.349	0.006	–0.557	< 0.001
Midwall shortening (%)	–0.717	< 0.001	–0.619	< 0.001	–0.723	< 0.001
Stress-corrected midwall shortening (%)	–0.755	< 0.001	–0.675	< 0.001	–0.759	< 0.001
E/E'	0.299	< 0.001	–0.158	0.228	0.293	0.002

HbA_{1c} = glycated haemoglobin, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, UACR = urine albumin creatinine ratio.

Table 5. Independent covariates of higher RWT in total population and type 1 and type 2 diabetes patients

	Total population (R2 = 0.69*)		Type 1 (R2 = 0.73*)		Type 2 (R2 = 0.66*)	
Covariate	β	***p*-value**	β	***p*-value**	β	***p*-value**
Systolic blood pressure (mmHg)	0.301	< 0.001	0.442	< 0.001	0.233	0.001
Low eGFR (ml/min/1.73 m²)	0.131	0.007	0.009	0.909	0.150	0.024
Low stress-corrected MWS (%)	0.239	< 0.001	0.493	< 0.001	0.156	0.017
Isovolumic relaxation time (ms)	0.170	0.001	0.180	0.041	0.155	0.016
LV mass/height$^{2.7}$	0.187	0.001	0.091	0.284	0.189	0.008
Circumferential end-systolic stress (dyne/cm²)	–0.584	< 0.001	–0.682	< 0.001	–0.602	< 0.001
Male gender	0.083	0.065	–0.009	0.905	0.123	0.051

eGFR = estimated glomerular filtration rate, MWS = midwall shortening, *$p < 0.001$.

LV geometry in diabetic populations from sub-Saharan Africa. Therefore, the present study is among the few to report on prevalence and covariates of abnormal LV geometry in diabetic sub-Saharan African patients.

The study has many interesting findings, adding to current knowledge on diabetic heart disease in Africans, in particular (1) that abnormal LV geometry is common in sub-Saharan African diabetic patients, (2) that concentric remodelling was the most prevalent abnormal LV geometric pattern in this population and associated with reduced LV myocardial contractility and delayed diastolic relaxation, and (3) that a simple algorithm combining everyday clinical and laboratory assessment may be used to identify diabetic patients with high risk of cardiac target-organ damage.

Our findings add to a previous report by Ojji *et al*. on Nigerians with type 2 diabetes.[21] In their study of 122 patients, abnormal LV geometry was found in 51% of patients, compared to 74% in the present study. Of note, the study by Ojji *et al*.[21] only included normotensive type 2 diabetes patients, and as demonstrated by our findings, hypertension was a strong covariate of having both LV hypertrophy and increased RWT, probably explaining the higher prevalence of abnormal LV geometry in the present study. As demonstrated, age and systolic blood pressure were the main confounders explaining the difference in LV structure between groups of patients with type 1 or type 2 diabetes.

Hypertension, in particular isolated systolic hypertension, increases in prevalence with aging, mainly as a consequence of arterial stiffening imposing increased load on the left ventricle. Older age has been documented to be particularly associated with increased RWT, and with LV hypertrophy when hypertension coexists.[22-24] However, despite differences in socio-demographic backgrounds, our results were comparable to those reported by Eguchi *et al*. from Japanese hypertensive patients with type 2 diabetes. In their study, including 161 patients, the prevalence of concentric remodelling, eccentric hypertrophy and concentric hypertrophy, respectively, were 29, 16 and 39%.[25]

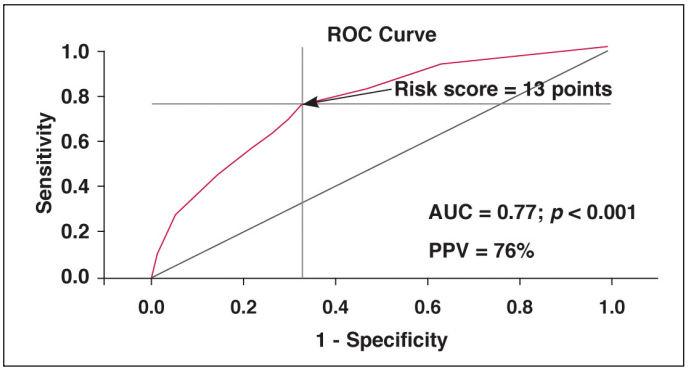

Figure 4. Receiver-operator characteristic (ROC) curve for the clinical risk score with best sensitivity (76%) and specificity (67%) in predicting high relative wall thickness. The cut-off value for the risk score (13 points) identified by the ROC analysis is indicated by an arrow. AUC = area under the curve, PPV = positive predictive value.

We found no previous echocardiographic study on LV geometric patterns performed among type 1 diabetes patients from sub-Saharan Africa, and our study is probably the first to describe LV geometry in such patients. As demonstrated by our results, abnormal LV geometry was found in 40% of type 1 diabetes patients. Specifically, 30% of type 1 diabetes patients had concentric remodelling, and this was the most common type of abnormal LV geometry in this group. All six type 1 diabetes patients (10%) with LV hypertrophy had eccentric LV hypertrophy.

Interestingly, none of the type 1 diabetes patients had concentric LV hypertrophy, the most common abnormal LV geometric pattern found among type 2 diabetes patients in the present study. This finding could probably be explained by the low prevalence of hypertension among type 1 diabetes patients in our study (18 vs 82%). Other investigators have reported a higher prevalence of LV hypertrophy among type 1 diabetes patients with nephropathy.[26]

Of note, in the present study population, all type 1 diabetes patients with LV hypertrophy also had albuminuria (results not shown), and albuminuria was identified as a main covariate of LV hypertrophy in multivariate analysis. The beneficial impact of renin–angiotensin inhibition on albuminuria and the prevention of overt renal failure has previously been demonstrated in type 1 diabetes patients with microalbuminuria.[27] Whether the prevention of progression to overt renal failure with the use of drugs that inhibit the renin–angiotensin system will also prevent progression to LV hypertrophy among type 1 diabetes patients is a question that needs to be answered in future prospective studies in Africans.

The finding that higher RWT was significantly associated with older age and higher blood pressure agree with previous reports from epidemiological studies in North American Indians.[3] Importantly though, as demonstrated by multivariate analysis in our study, independent associations between increased RWT and measures of systolic and diastolic LV function were found irrespective of presence or absence of LV hypertrophy or hypertension. This is an important finding because it emphasises the need to further stratify patients into the different LV geometric patterns, rather than by presence or absence of LV hypertrophy alone. The finding is particularly important in the African diabetes context, as concentric remodelling (increased RWT with normal LVMI) was found to be the most common abnormal LV geometric pattern in the present study, as also previously reported among African American hypertensive patients.[4]

In 884 children and adolescents with a high prevalence of obesity, Di Bonito *et al*. found that higher triglyceride-to-HDL cholesterol ratio independently predicted higher RWT and concentric LV hypertrophy.[28] In our study, lower serum HDL cholesterol levels, but not triglyceride-to-HDL cholesterol ratio, were associated with higher RWT in type 2 diabetes patients, only in univariate analysis. The differential findings probably reflect differences in prevalence of obesity and degree of myocardial fat storage between the two populations.[29]

In the LIFE study, concentric remodelling was associated with a three and eight times increased risk of stroke and cardiovascular death after 4.8 years of follow up, respectively.[30] So, in a way, our findings may be explaining the link between the increased prevalence of congestive heart failure and stroke seen among black diabetic patients.[31]

Of note, an independent association between gender and measures of LV geometry was not found in the present study population, partly contrasting with findings in African Americans participating in the Atherosclerosis Risk in Community (ARIC) study, which reported that diabetic women had more concentric LV geometry, but similar prevalence of LV hypertrophy as men.[32]

We have shown that a simple algorithm using every-day clinical and laboratory tests (type of diabetes, hypertension, obesity and albuminuria) may be used to identify three out of four high-risk diabetic patients with increased RWT. This is very important in a setting such as Tanzania where echocardiography is not readily available. Of note, following this algorithm, a patient with type 2 diabetes with any of the other three risk factors, or a type 1 diabetes patient having any two of the other three risk factors will have a 76% chance of having cardiac target-organ damage as well.

Conclusion

We have shown that abnormal LV geometry was common in this diabetic population. In particular, increased RWT was present in 58% of patients and demonstrated as a marker of subclinical cardiac target-organ damage. Furthermore, using the clinical risk factors, type of diabetes, hypertension, obesity and albuminuria, 76% of diabetic patients with increased RWT can be identified.

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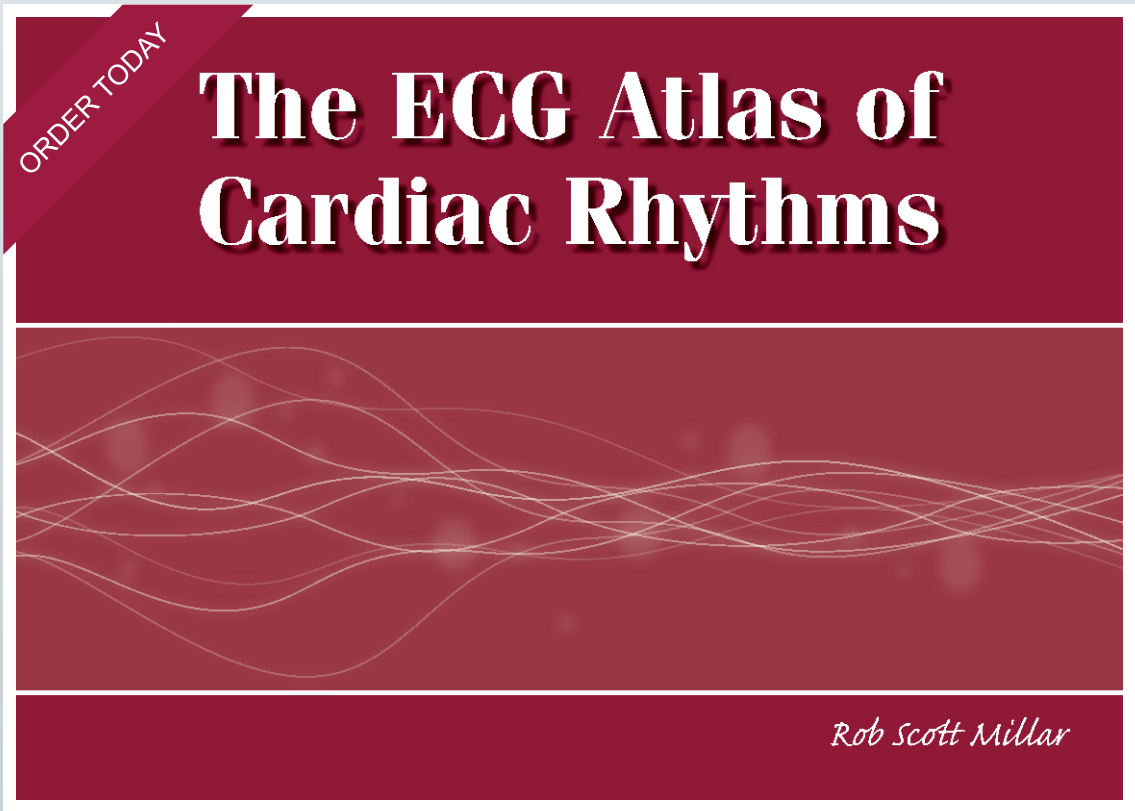

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