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From the Editor's Desk

This edition of the journal looks at a number of subjects, from the vascular effects of pioglitazone and homocysteine, to phototherapy in diabetic foot disease, and an explanation of the bioecological model, among others.

Tugrul *et al.* (page 24) studied aortic contractility in the presence of pioglitazone and losartan. Their research in rats showed a decreased contractile response to phenylephrine when these drugs were present. This supports the notion of the pleiotropic effects of PPAR agonists,[1] and may indicate additional beneficial effects of pioglitazone.

Hapunda and co-authors (page 11) present an excellent exposition of the bioecological model with which one can obtain a holistic view of diabetes care, from the individual to the systems that operate around that individual. This article gives one an understanding of the bioecological model and the areas of intervention.

Sithole and Abrahamse (page 4) show us the tremendous value of podiatric interventions, including phototherapy, in the management of diabetic foot ulcer disease. Foot ulcers have a great impact on the patient's quality of life and may be the precursor to worse outcomes, such as severe sepsis and amputations.[2] This article also shows very clearly that the podiatrist is of crucial importance in the management of diabetic foot ulcer disease.

Zand Parsa and Jahanshahi (page 29) add to the debate around measurements of obesity and their relationship to cardiovascular risk.[3] They re-affirm the utility of waist:hip ratio measurements as an indicator of cardiovascular risk, and also highlight the interesting negative correlation that they found with body mass index. They discuss the implications and the possible reasons for this.

Sengwayo *et al.* (page 33) looked for an association between homocysteine level and the metabolic syndrome. This would have provided a link between vascular dysfunction and elements of the metabolic syndrome, which has been postulated before.[4] They found a link only to hypertension. This needs to be investigated further.

Pillay and Aldous (page 18) show how low-resourced diabetes clinics can make a difference to their quality of care by restructuring the clinic to emphasise a multidisciplinary approach to care and the use of proper documentation. This is an important theme in the work of these authors.[5] Poor diabetes care can lead to many complications and a high burden of disease for the individual as well as the healthcare system.

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Podiatric interventions and phototherapy in the management of chronic diabetic foot ulceration: a review to compare the average healing time

N SITHOLE, H ABRAHAMSE

Abstract

Diabetic foot ulceration is a serious complication of diabetes mellitus and an important risk factor for lower-limb amputations. Diabetes is characterised by chronic hyperglycaemia related to the resistance of target cells to the action of insulin, which leads to degenerative disorders caused by macro- and microangiopathy, and neuropathy. These factors favour the occurrence of lower-limb ulcers and delay their healing. The slow healing rate of chronic diabetic foot ulceration has a negative impact on the patient's quality of life. There is a need therefore for the development of new treatment modalities to improve the healing rate and outcomes of diabetic ulcerations.

The management and treatment of chronic diabetic ulcerations can last an extended period due to the lack of response to treatment or the general nature of the ulcer. Current podiatric protocols for the management of chronic ulcers affecting the lower limb involve a dynamic approach, which includes mechanical debridement of granulation and dead tissue, antibiotics to treat infection, change of footwear, mechanical off-loading using total-contact casts and orthotic devices, as well as foot-care education.

Phototherapy is an alternative treatment modality that is under investigation for the management of chronic diabetic foot ulceration. It has been found to significantly increase the healing rate of ulcers when used in combination with other conventional treatments. The continuous management and on-going surveillance and monitoring of chronic diabetic foot ulcers with various combination therapies, including phototherapy, may improve the healing time as so improve a patient's quality of life and physical activities.

The aim of this review is to compare the average healing time of diabetic foot ulcers when treated with standard podiatric treatment protocols and when treated in combination with phototherapy in terms of diabetic foot-ulcer management.

Keywords: diabetes, foot ulcers, wound healing, laser, phototherapy, off-loading, wound debridement.

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Introduction

Diabetes mellitus is a common metabolic condition that is increasing in prevalence worldwide. The estimates by the International Diabetes Federation in 2009 suggested that the number of adults with diabetes in the world will increase by 54%, from 284.6 million in 2010 to 438.4 million in 2030.

In sub-Saharan Africa in 2010, the projected growth in incidence of diabetes was 98%, with the prevalence of type 2 diabetes rising quickly.[1] In South Africa in 2003, a prevalence figure was noted of 3.4% among the 24 million adults between the ages of 20 and 79 years. However in 2015, there were 2.28 million (7.0%) adult diabetes cases noted in South Africa.[2] This drastic increase presents a substantial public health and socio-economic burden to this country in the face of scarce resources.[3]

Type 2 diabetes is characterised by chronic hyperglycaemia related to the resistance of target cells to the action of insulin, which leads to degenerative disorders caused by macro- and microangiopathy, and neuropathy.[4,5] These factors favour the occurrence of disease complications, such as lower-limb ulcers and delayed healing.[5,6]

Diabetic foot ulcers (DFUs) are estimated to occur in 15% of all patients with diabetes and precede 84% of all diabetes-related lower-leg amputations. These ulcers are a major cause of hospital admissions for people with diabetes in the developed world and are a major morbidity associated with diabetes, often leading to pain, suffering, and an overall poor quality of life for the patient.[7]

Classification of DFUs

Diabetic foot ulcers can result from multiple factors and are therefore classified according to the relative contribution of late diabetic complications of peripheral neuropathy and vascular diseases.[8] Most diabetic lower-limb ulcers occur in the presence of peripheral neuropathy, foot deformity and trauma, and these are called neuropathic ulcers. Peripheral vascular disease, resulting in neuro-ischaemic ulcers and infection, is believed to be the complicating factor that prevents or delays ulcer healing.[9] The literature suggests that the nature of chronic diabetic foot ulcerations disables the normal stages of healing, which in turn induces a state of pathological inflammation. This then results in the overall healing process becoming incomplete or delayed.[10]

Diabetic ulcers are also classified according to their severity or in grades using the universally accepted validated tools such as the Wagner and University of Texas classifications. Wagner's classification grades 0–5 divides ulcers from superficial or deep ulcers up to gangrene of the foot. The University of Texas classification stages 1–5 adds the presence of infection, ischaemia, or both infection and ischaemia together.[11,12] These classifications are important as we need to adequately describe the ulcers that we treat in order to review a patient's outcome.[11]

General DFU management

Management of the diabetic foot often requires a holistic approach, which involves a focused multidisciplinary team consisting of a wound nurse, podiatrist, vascular surgeon, endocrinologist and other allied healthcare professionals.[6,9,13-16] However, the overall wound management of chronic DFUs can last for extended periods without any healing response, due to the multiple complex pathophysiological mechanisms involved in patients suffering from diabetes. These can involve hypoxia, dysfunction in the fibroblasts and epidermal cells, impaired angiogenesis and neovascularisation, high levels of metalloproteases, damage from oxygen radicals and advanced glycation end-products.[10,17] Peripheral neuropathy can also contribute to the development and impaired healing of DFUs. Neuropeptides such as nerve growth factor, substance P and calcitonin gene-related peptide, and sensory nerves are needed to induce wound healing, however their low levels in diabetic patients have been associated with the development of DFUs.[10]

Despite all these challenges, there is increasing cause for optimism in the treatment of diabetic ulcers. This is due to the enhanced understanding and correction of these pathogenic factors, combined with stricter adherence to standards of care and technological breakthroughs in biological agents, and this is giving new hope to the problem of impaired healing of diabetic ulcers.[18]

Key message: Patients with diabetes mellitus develop foot problems, such as neuropathy, infections, ulcers and vascular diseases, which require an integrated multidisciplinary approach to address all these problems. Failure to adequately treat and resolve these problems can be due to the multiple complex pathophysiological mechanisms involved with diabetes, which is a multisystem disease.

Podiatric DFU management

A podiatrist's approach to the treatment of DFUs consists of an overall assessment of the structure and function of the lower limb by performing biomechanical evaluation, and gait and plantar pressure analysis. Thus podiatric management and involvement can prevent diabetic ulcer recurrence in patients through the use of various off-loading techniques and diabetic patient foot education.[15]

Podiatrists also provide patients with local wound care, which involves debridement of necrotic tissue and callus, cleansing with suitable solutions, wound dressings, topical or oral antibiotics when infection is present, and revascularisation.[9,13-15,19] This is the general standard of wound management that is implemented in diabetic ulcer wound-care clinics and it involves a multidisciplinary team, as alluded to earlier.

Key message: Podiatrists are professionals trained to assess and implement treatment for diabetic lower limb and foot problems, including diabetic foot ulcers. Podiatrists manage and treat diabetic foot through wound debridement, appropriate wound cleansing and dressings, off-loading, infection control and education.

Off-loading

Off-loading is an essential tool that is used in the healing of DFUs, particularly in cases where a patient has a plantar neuropathic ulcer (Fig. 1), or for secondary prevention in patients with healed ulceration but who have foot deformity.[9,19] Different off-loading techniques are commonly used to protect a diabetic foot from excessive pressure and other forms of trauma that sometimes lead to diabetic ulceration or even worse, amputation. These can be grouped into casting, footwear-related and surgical off-loading techniques, and other.[20] Off-loading techniques used by podiatrists in South Africa and overseas include felt padding, prescription orthotics and insoles, removable cast walkers and total-contact casting (Figs 2–5).[9,14,15]

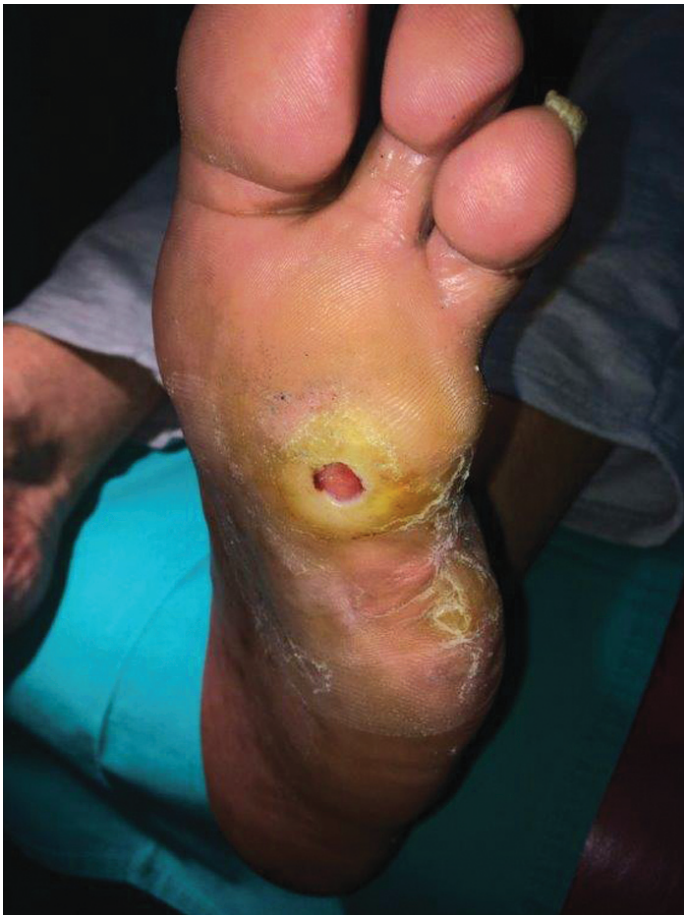

Fig. 1. Diabetic neuropathic ulcer.

Key message: Off-loading can be defined as a treatment modality where practitioners try to protect the foot or reduce excessive pressure that can lead to ulceration or even amputation in the diabetic foot. Different off-loading techniques can be implemented with varying results/success, with some techniques better than others.

Footwear and orthotic devices for the prevention of DFU

Therapeutic footwear in combination with custom-made orthotic devices (Fig. 2) are considered the primary means of protecting the foot from excessive plantar pressure during walking, thus reducing the incidence of ulceration.

In a study by Mueller *et al.* investigating the effect of total-contact cast inserts (TCIs) and metatarsal pads (MPs) on metatarsal peak pressures and pressure–time integrals, it was found that the TCI

Fig. 2. Custom-made orthoses.

and MP caused a substantial and additive reduction in pressure (29 to 47%) under the metatarsal heads of the feet by increasing the contact area of weight-bearing forces when compared to wearing shoes alone. In addition, it was reported that the MP reduced the pressure at the metatarsal heads of feet by off-loading the soft tissue and bone structures proximal to the metatarsal heads.[21]

These findings are similar to a study done by Tong and Ng who investigated the amount of pressure reduction that occurred in feet when using different types of padding and four insole materials that are commonly used in podiatry. In this study it was found that all four commonly used materials, Slow Recovery Poron (SRP), Poron, Poron + Plastazote firm (PPF) and Poron + Plastazote soft (PPS), were able to reduce pressure across the whole foot, with PPF achieving the most significant result of 28% pressure reduction. The subjects in this study were also tested with a semi-compressed felt metatarsal pad (Fig. 3) with an aperture on the first metatarsophalangeal joint of both feet. The peak pressure in this area showed a significant reduction of 37% compared to a 29% decrease when PPF was used alone.[22]

Overall, both studies noted that the human foot generally has increased pressure at the periphery of the aperture site, which, if not corrected, can cause harmful skin breakdown, and in the insensate feet of diabetic patients, this can sometimes lead to severe ulceration. In addition, the pressure responses varied in the two studies, suggesting that pressure reduction in terms of using footwear and orthotic devices is highly dependent upon the condition of the patient's feet and the patients' health status, as well as differences in metatarsal pad material used, including its size and shape.

Although there are indications that therapeutic footwear may be effective in secondary prevention of DFUs,[8] according to some literature, there are no experimental studies that report on the role of therapeutic footwear in primary ulcer prevention compared to normal footwear. This conclusion only came about because one randomised control trial found no effect of therapeutic footwear in the secondary prevention of ulcers.[8,20] However other literature suggests that various designs of therapeutic footwear such as rocker bottom outsole and half-shoes can effectively off-load at-risk foot regions, thus preventing ulcer formation or recurrence.[8]

Key message: Therapeutic footwear and custom-made orthoses are generally used by podiatrists to prevent the secondary occurrence of DFU.

Total-contact casting

Over the years, total-contact casting (TCC) has been known to be more effective in the treatment of non-infected diabetic plantar neuropathic ulcers, compared to other removable off-loading devices. Studies by Sambrook *et al.* noted that TCC has been shown to reduce plantar pressure by 84 to 94%, and increase healing rates and treatment time of plantar ulcers.[23]

However, TCC is a difficult and time-consuming treatment for podiatrists to apply and generally there is low patient tolerance, with a number of side effects associated with its application. Therefore most clinicians prefer to not use this technique and rather prescribe various other off-loading techniques that are far easier to apply, such as felt padding, removable cast walkers (RCW), therapeutic footwear and orthotic devices.[24]

Studies performed by Fife *et al.* using real-world data from a large wound-care registry found that only 6% of DFU patients received TCC.[25] Some years later in their reflective analysis, Fife *et al.* found that in over 25 000 patients with diabetes, only 3.7% of eligible ulcers received TCC.[26] Currently there are no data on the use of TCC for the management of DFUs in South Africa.

Alternative approaches of non-removable off-loading devices that are far more effective have been developed in recent years. These are a substitute for the classic Plaster-of-Paris total-contact casting. Armstrong and colleagues performed a study to evaluate the effectiveness of a RCW (Fig. 4) and an 'instant' total-contact cast (iTCC) (Fig. 5) in the healing of neuropathic DFUs.[27] Patients with foot ulcers that were cast using iTCC reported more significant ulcer healing rates of 82.6% over a 12-week period than the 51.9% healing of patients who received RCW.

Fig. 3. Semi-compressed felt metatarsal pads.

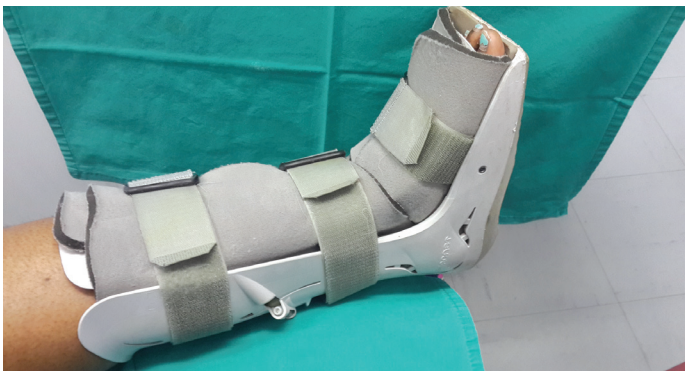

Fig. 4. Removable cast walker.

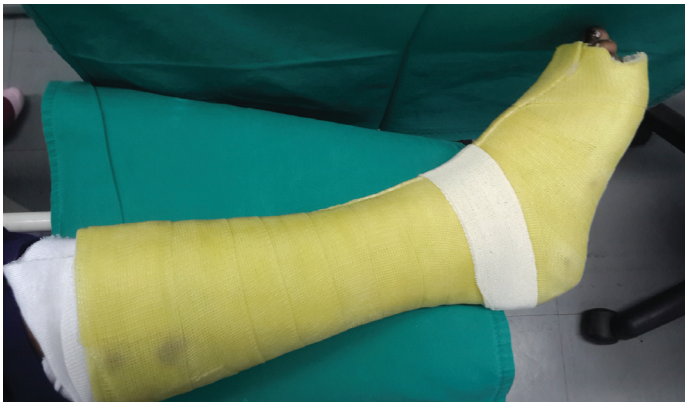

Fig. 5. Total contact cast.

Similarly, in a study conducted by Faglia *et al.* over a 90-day period where the efficacy of RCW and a non-removable fibreglass off-bearing cast (TCC) were compared in DFU healing, it was reported that 73.9% of patients in the TCC group and 72.7% in the RCW group achieved complete healing.[28] Overall, these studies show that whether the off-loading device is removable or non-removable, it can be used effectively to redistribute pressure on the plantar aspect of the foot. However results are dependent on the patient's compliance to constantly wear removable devices.

Key message: Total-contact casting has been shown to be effective in redistributing pressure in the plantar aspect of the foot and so either prevents ulcers from re-occurring or promotes healing of current DFUs.

Wound debridement

In wound-healing clinics, various types of debridement techniques can be used by podiatrists to treat DFUs, such as surgical and sharp debridement, mechanical, autolytic and enzymatic debridement, and larval debridement.[29] Debridement is the most important step towards achieving chronic diabetic wound healing, as it transforms chronic wounds into acute wounds.[30]

Unlike acute wounds, chronic diabetic ulcers seldom follow the normal pattern of repair due to various physiological factors such as hypoxia, dysfunction in the fibroblasts and epidermal cells, impaired angiogenesis and neovascularisation, high levels of metalloproteases, damage from oxygen radicals and advanced glycation end-products, which delay wound healing.[7,31] In addition, there is also sometimes an accumulation of non-viable tissue (calluses) and slough with excess exudate, which also encourages bacterial colonisation (biofilm), promoting the risk of infection and so preventing healing.[31,32]

Sharp debridement (scalpel debridement) helps to break down bacterial colonies, thus reducing the bacterial load of an ulcer even in the absence of overt infection, and so promotes the release of growth factors to aid the healing process.[32] When combined with standard or advanced therapies that are currently used in ulcer treatment, the net rate of healing is increased.[32]

Williams and colleagues evaluated the effect of sharp debridement on the progression of recalcitrant chronic venous leg ulcers. This study concluded that sharp debridement was effective in stimulating the healing of ulcers. It was conducted over a 12-month period and already at four weeks post-debridement, some positive results were observed; ulcers showed a 6-cm^2 reduction within the mean ulcer surface area (MSA) versus a 1-cm^2 reduction in the control group. However, it was noted that the reduction in MSA between the study groups over the entire period was not statistically significant. Nevertheless, wounds after debridement alone are capable of regressing in 57% of the days between visits because there is balance shift favouring the biofilm, even though the rate of healing immediately after debridement is more rapid.[32]

It has been suggested that frequent debridement of DFUs and chronic venous leg ulcers, as part of wound treatment, may increase wound healing rates and closure of the ulcer.[33] If debridement is done in a sequential fashion, it will avoid the re-establishment of microbial biofilm growth and tissue devitalisation, which is responsible for delayed healing of ulcers.[7,32]

Wilcox and colleagues investigated the frequency of debridement and the time to heal for different types of ulcers, including DFUs and chronic venous ulcers. This study noted that the median time to heal after weekly or more frequent debridement for DFU was 21 days, compared to 64 days when debridement frequency was in the range of every one to two weeks, and 76 days when debridement was once every two weeks or more.[34]

Furthermore, in a study performed by Ahmad and colleagues, which assessed the efficacy of radical debridement and skin grafting in treating DFUs, compared with other conservative wound treatments (such as the use of dressings, negative-pressure wound therapy and hyperbaric oxygen), the results showed a 100% skin graft take in 80% of the patients on day four after surgery. Debridement in this study was performed three times a week, every second day, and the amount of granulation tissue was assessed before skin grafting. The mean healing time and hospital stay was lower in the skin-graft group compared to the control group (4.0 ± 1.5 vs 10.0 ± 1.0 weeks).[31] These findings suggest that aggressive and repeated debridement definitely does increase ulcer healing rates of chronic wounds.

Both off-loading and debridement methods are regularly practised by podiatrists to promote the healing process of diabetic lower-limb ulcers. Additionally, selecting the right type of wound dressing is also important to aid the healing process, and this is also dependant on the characteristics of the individual ulcer that is receiving treatment.[9,13,14,19]

Debridement practises offer an opportunity for additional antibiotic interventions, applied topically and/or systemically, which temporarily disrupt biofilm defence colonies, forcing microbes to become more susceptible to these interventional treatments as well as the host's immune defenses.[32] A summary of these clinical studies is presented in Table 1.

Key message: Mechanical or sharp debridement is one of the essential treatment procedures in podiatry with which chronic inflammation can be converted to acute inflammation to promote DFU healing.

Phototherapy

Phototherapy is a therapeutic modality that involves the application of laser light, at a particular wavelength and at low intensities, to tissue to stimulate various biological processes.[16,35] Low-level laser therapy (LLLT) is widely used to accelerate tissue repair in surgery, dentistry, dermatology, somatology, pain management and ulcer

Table 1. Clinical trials on diabetic lower-limb ulcer treatment with podiatric interventions

Study	Study design	Participants	Intervention	Outcome
Armstrong *et al.* (2005)	A randomised controlled trial	50 patients with University of Texas grade 1A DFUs	Off-loading with RCW and iTTC. Evaluated weekly for 12 weeks	A significantly higher proportion of patients healed at 12 weeks in the iTTC group than in the RCW group [82.6%/19 patients vs 51.9%/14 patients, p = 0.02 or 1.8 (95% CI : 1.12.9)]
Faglia *et al.* (2010)	A randomised controlled trial	45 diabetic patients with non-ischaemic and non-infected neuropathic plantar ulcers	Off-loading with a non-removable fibreglass off-bearing cast (TCC) and walker cast. Treatment duration was 90 days	The mean duration of healing time was 35.3 ± 3.1 days in the TCC group and 39.7 ± 4.2 days in the Stabil-D group (p = 0.708)
Wilcox *et al.* (2013)	Retrospective cohort study	Sample of 154 644 patients with 312 744 wounds of all causes; DFUs (19.0%), venous leg ulcers (26.1%), and pressure ulcers (16.2%). From 525 wound-care centres from 1 June 2008 to 31 June 2012	Debridement at different frequencies	The median time to heal after weekly or more frequent debridement for DFUs was 21 days compared to 64 days when debridement frequency was in a range of every 1–2 weeks, and 76 days when debridement was once every 2 weeks or more
Ahmad *et al.* (2012)	Retrospective cohort study	Medical notes for 30 patients who underwent skin grafting for DFU (graft group) and 30 other patients, who were treated conservatively (control group)	Radical debridement to prepare the wound bed for grafting	A 100% skin graft take was recorded in 80% of the patients on day 4 postoperatively; 93% of patients in the graft group healed completely. The mean healing time and hospital stay was lower in the skin-graft group compared to the control group (4.0 ± 1.5 vs 10.0 ± 1.0 weeks)

healing.[36] Unlike high-intensity medical lasers, which are used to cut and coagulate tissues, LLLT involves the use of medical lasers that operate at low intensities, which instead of causing damage, promote healing.[37]

LLLT in the promotion of wound healing

The exact mechanism of action of LLLT is not completely understood, however in some *in vitro* studies it has been noted that LLLT supplies direct biostimulative light energy to body cells.[38] For LLLT to be effective, the light must be absorbed by the targeted tissue.[37,39]

Photon energy is absorbed by photo-acceptors or chromophores within the cells. The main photo-acceptor in cells is cytochrome c oxidase, which is found inside the cell mitochondria.[35] When the mitochondrion absorbs photons, it is stimulated to produce more energy-rich adenosine triphosphate (ATP), which in turn temporarily increases the cell membrane permeability to absorb calcium ions, enhancing cellular activity and repair.[35] In this way, when absorbed, photons induce cellular changes, and tissue repair and healing is accelerated.[37] Since chronic ulcers such as diabetic ulcers do not follow the normal pathway of healing, phototherapy has been shown to be a promising form of treatment to promote the ulcer healing process.[16]

Studies using LLLT have shown it to positively stimulate diabetic ulcer fibroblasts, which resulted in promoted wound healing through increased viability, proliferation of ATP, growth factors and cytokines, and nitric oxide stimulation, as well as decreased cellular damage and pro-inflammatory cytokine expression.[16,38,40] According to the literature, LLLT transforms fibroblasts into myofibroblasts, which are essential for the development of granulation tissue and so promotes wound contraction.[37,39]

In a double-blinded, randomised, placebo-controlled experimental trial, Minatel *et al.* treated the chronic diabetic leg ulcers of 23 patients that were unresponsive to other forms of treatment. Thirteen ulcers were treated with phototherapy (combined 660 and 890 nm) twice a week until healed, or for a maximum period of three months. The rest were sham irradiated (10 ulcers). In the group of ulcers that were irradiated, 58.3% resolved completely, and 75% of the ulcers achieved 90 to 100% healing by day 90.[5]

In a clinical study by Mokmeli and colleagues, which determined the effect of local and intravenous LLLT for the healing of 74 DFUs, the results showed that 62.2% of the patients' ulcers completely healed, 12.2% of the ulcers healed by more than half, and only 8.1% of ulcers healed less than half. However, 12.2% of the patients did not complete their treatment (which only consisted of five sessions of LLLT). Excluding the wounds that were found to be in stage 5, more than 80% of each categorised stage were found to have been almost completely healed (by more than 50%) within a two-month period.[41]

In their study, Kajagar and colleagues compared diabetic ulcer healing in 68 patients. These patients were randomised into a LLLT-plus-conventional care group, which was compared with conventional care alone. On the basis of the ulcer size, the duration of exposure was calculated to deliver 2–4 J/cm^2 at 60 mW, 5 KHz daily for 15 days. The ulcer floor and edges were irradiated. A significant percentage of ulcer reduction in the LLLT group compared with conventional care alone was noted: 40.24±6.30 mm^2 in the study group and 11.87±4.28 mm^2 in control group (p<0.001, Z=7.08).[42]

According to the literature, acute inflammation is a vital stage in healing and for chronic ulcers this must be induced by debridement in order for the healing to progress. Mechanical or sharp debridement is one of the essential treatment procedures in podiatry with which chronic inflammation can be converted to acute inflammation.[14,15] Once acute inflammation has been achieved, it should then be followed by LLLT to stimulate the proliferation

Table 2. Clinical trials on lower-limb ulcer treatment with LLT in diabetic ulcers

Study	Study design	Participants	Intervention	Outcome
Kazemi-Khoo (2006)	Prospective cohort study	7 type 2 diabetes patients with grades 2 and 3 diabetic foot ulcers	Red light (660 nm; power: 25 MW; 0.6–1 J/cm²) and ulcer margins with infra-red laser (980 nm; power: 200 MW; 4–6 J/cm²) along with intravenous laser irradiation with red light laser (650 nm; power: 1.5 MW) for 15–20 min, in addition to laser acupuncture with infrared laser (1 J/cm²). Sessions were every other day for 10–15 sessions (route 1) and then continuing the course twice weekly (route 2) until complete recovery was achieved	Complete recovery was achieved in all cases and there was no relapse after an average of about 19 sessions. Only 1 case took a total of 26 sessions (route 1).
Minatel *et al*. (2009)	Randomised, placebo-controlled, double-blinded trial	14 patients with 23 chronic diabetic ulcers	LLLT: 660 nm and 890 nm, 3 J/cm², 30 sec/5 cm² twice a week for 90 days/until healed	LLLT group had more granulation (day 30: 56%) and faster healing (day 30: 79.2%), 58.3% healed fully (1 ulcer placebo group); 75% ulcer healed 90–100% day 90 (1 ulcer placebo group)
Mokmeli *et al.* (2010)	Prospective cohort study	74 DFUs	LLLT: 650 nm and 860-nm laser, with total energy density of 3.6 J/cm² plus intravenous laser therapy (IVL) with 2.5-MW, 650-nm laser used for 30 minutes	Excluding the wounds that were found to be in stage 5, more than 80% of each categorised stage were found to have been almost completely healed (by more than 50%) within a 2-month period
Kajagar *et al.* (2012)	Randomised controlled trial	68 patients with chronic DFUs (grade 1)	Daily treatment for 15 days, 2–4-J/cm² power, 60-mW frequency, 5 kHz	Significant reduction of percentage of ulcer area in the LLLT group

of endothelial cells and fibroblasts, accelerating the development of granulation tissue over which epidermal cells migrate and so enhance wound healing.[37]

Despite the fact that LLLT is not an established treatment modality for ulceration in South Africa, a number of studies, case reports and clinical trials with humans have shown good ulcer healing outcomes using LLLT. Beckmann and colleagues conducted a systemic review in 2014 of the relevant literature on LLLT for the treatment of DFUs and found that several clinical studies had been published between 1998 and 2011, suggesting that LLLT promotes wound healing of diabetic ulceration.[12] A summary of these clinical trials is presented in Table 2.

Key message: Once acute inflammation has been induced in DFUs by mechanical or sharp debridement, the healing process can be further promoted by LLLT, which stimulates cellular proliferation and wound healing.

Phototherapy, bactericidal effects and cellular repair enhance wound healing

Various wavelengths are used for different applications in phototherapy as they have different depths of penetration into human tissue. Visible red, infra-red and near infra-red have been demonstrated to penetrate deep tissue and are absorbed by cytochrome c oxidase, compared to violet and blue spectrum lasers.[39,43] When blue laser light is absorbed by flavins (flavoproteins) and porphyrins that lack transition metal coordinating, these molecules have been shown to have bactericidal effects through the production of reactive free radicals, which destroy bacteria.[35,37-39]

A number of studies have found that, at different wavelengths, blue light laser is bactericidal to different infectious organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Propionibacterium acne* and *Pseudomonas aeruginosa*.[16] Enwemeka *et al.* found that blue light (470 nm) was able to kill MRSA *in vitro*.[44] Lipovsky *et al*. suggested that high-intensity visible light in the range of 400–1 000 nm is bactericidal to *S aureus*, *P aeruginosa* and *Escherichia coli*, to name a few.[45] Irradiation at a wavelength of 408 nm was proposed by Ankri and colleagues in treating infected wounds to clear an infection, followed by irradiation at 730 nm to speed up the healing process.[43]

According to the literature, red as well as blue light lasers improve perfusion by releasing nitric oxide (NO) from nitrosyl complexes with haemoglobin, enhanced epithelialisation and elevated keratin-10 mRNA levels.[38] It has been discovered that the activity of cytochrome c oxidase is inhibited by NO and this was initially seen as an imperfection.[36] However blue light also facilitates the recovery of mitochondria inhibited by NO gas by releasing NO from the mitochondrial complexes. Therefore improved wound healing via the NO pathway induces endothelial cell migration by activating growth factors, resulting in an increase in keratin expression.[38] This shows that a combination of red and blue light lasers can be used to treat infection to promote and enhance the healing process of infected DFUs, since infection plays a role in delaying the wound healing process.

Key message: Phototherapy can enhance wound healing of DFUs, since it exhibits bactericidal effects as well as stimulating cellular repair and growth.

Conclusion

Diabetic foot ulceration still proves to be a difficult condition to manage and generally has a negative impact on the patient's

quality of life. Identifying a treatment modality to help resolve this complication remains a difficult task in clinical practice. However a number of clinical trials suggest LLLT as an alternative and promising treatment modality that, when combined with other conventional treatments, has shown potential in improving the healing rate of chronic diabetic ulcerations. It is therefore essential to recognise that with the use of LLLT in podiatry and other wound clinics, the treatment or management of chronic diabetic lower-limb ulcerations can be reduced to an average of 19 sessions to achieve a complete recovery,[43] compared to 40 sessions using conventional treatments alone.[5,46] This could lead to reduced hospital admissions for people with diabetic ulcers and lighten the substantial public health and socio-economic burden to our country. Further investigations are necessary to obtain conclusive evidence of low-level laser in treating diabetic foot ulcers in South Africa.

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Applying the bioecological model to understand factors contributing to psychosocial well-being and healthcare of children and adolescents with diabetes mellitus

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Abstract

We discuss the bioecological model of Urie Bronfrenbreener and its application to diabetes care and the psychosocial well-being of children with diabetes in sub-Saharan Africa. Using empirical evidence, this article demonstrates that the bioecological model provides an important framework for understanding diabetes care needs and the interventional strategies required to enhance the well-being of children living with diabetes. It also discusses clinical and research implications. The advantage of applying the bioecological model in drawing up interventional strategies for those living with diabetes is that it targets large-scale public health interventions, unlike medical intervention, which focuses on a single individual.

Keywords: bioecological model, PPCT, children, adolescents, diabetes care, psychosocial well-being

Introduction

Healthcare providers, psychologists, parents and significant others, such as teachers, require comprehensive knowledge of social and biological factors that contribute to the personal development and healthcare of children and adolescents with diabetes mellitus. Diabetes mellitus is a metabolic disorder of multiple aetiologies, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action or both.[1,2]

One framework, which could help improve knowledge on environmental and biological factors that contribute to the development, healthcare and psychosocial well-being of children living with chronic illness such as diabetes mellitus is the bioecological model of Urie Bronfenbrenner.[3] This model could help researchers and healthcare practitioners understand a phenomenon within a larger context, in this case a framework for understanding the factors that produce and maintain health and health-related issues in diabetes. The bioecological model allows the identification of strategic points of interventions and to understand how social problems are produced and sustained within and across the various ecological systems.

Research evidence indicates that the most efficient preventative and interventional strategies for childhood problems consider the context in which a child lives, the interactions a child has with other people, and the influence of institutions and policies in the immediate and wider environment.[4] These ecologies are considered to influence a developing child.[5] As a result, it is useful to understand how the bioecological model can be used to understand the needs of children with diabetes.

The aim of this article is to discuss the application of the bioecological model to diabetes care and psychosocial well-being in children and adolescents with diabetes in sub-Saharan Africa. We review the ecological model based on the interrelationships in the process–person–context time model concept of the bioecological theory.[6] Then we discuss how the bioecological model can be applied to understanding diabetes care and psychosocial issues that affect children with diabetes within the sub-Saharan African context. Finally, clinical and research implications are discussed.

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The bioecological model

The bioecological theory of development posits that human development is a transactional process, influenced by an individual's interactions with various aspects and spheres of the environment.[7] The bioecological theory has four major components: process, person, context and time, also known as the process–person–context–time (PPCT) model.[8]

Process

The proximal or near processes involve all sorts of transactions between the child and the immediate surroundings that are responsible for the development of the child's competence and general well-being.[5] Proximal processes are near contexts to a child, involving a reciprocal interaction between a child and the environment. It is a bidirectional relationship between the child and the environment.

To be effective (contribute to child's competence and well-being), the transaction between the child and the environment must occur on a fairly regular basis over an extended period of time in a reciprocal manner. The transactions must be enduring, and participating in such interactive processes over time generates the ability, motivation and knowledge necessary for development.

Therefore, proximal processes are an important engine of

development.[7] These proximal processes drive development and are often seen as either protective or preventative systems, for example parental warmth, affection and discipline strategies. The form, power, content and direction of the proximal processes affecting development vary systematically as a joint function of the characteristics of the developing person and environment.[6]

Other than proximal processes, distal processes are at work in the life of a child with diabetes. Distal processes involve a unidirectional transaction between the child and environment, incorporating persons, objects and factors away from the centre of the child. To have an effect on the child, distal processes should have an enduring interaction with the child. Examples of distal processes may include the family's ability to support the child financially or emotionally.

Person

The person component of the model centres on the biological and genetic aspects of a child, including the personal characteristics that a child brings into any social situation.[9] The characteristic that a child brings in any situation can be divided in to three types: demand, resource and force characteristics.[6] Demand characteristics relate to 'personal stimulus', those that act as an immediate stimulus to another person, such as age, gender, skin colour, coping skills, reasoning and physical appearance. These types of characteristics may influence initial interactions because of the expectations formed immediately. Therefore, to some extent, the degree and nature of interactions involving family members, caregivers or peers is partially determined by the characteristics of the child itself.

Resource characteristics relate to mental and emotional resources such as past experiences, skills and intelligence and also to social and material access.[5] Force characteristics are those that have to do with differences of temperament, motivation and persistence among others.[6] Two children may have equal resource characteristics, but their developmental trajectories will be quite different if one is motivated to succeed and persists in tasks.[6]

Context

The context is the best-known component of the bioecological model and perhaps the most important of all four components in conceptualising and designing interventional studies in child development.[5] The context contains four distinct systems: micro-, meso-, exo- and macrosystems and each has either a direct or indirect influence on the child's development. The four systems within the framework of diabetes are depicted in the PPCT framework in Table 1.

The first system (the microsystem) is any environment such as home, school or peer group in which a person spends a good deal of time.[6] The second system is the mesosystem, which focuses on the connections between two or more systems within the microsystem. At this level, the model proposes that socialisation is influenced by those who interact with the child, such as schools, peers and neighbourhood. The systems here are believed to interact; for example, the home environment of the child can influence what happens in the playground with other children.

The exosystem is the third layer and looks at the context within a developing child's environment that the child does not directly encounter but impacts on the development. A decision to adjust the work schedule for a parent can, for example, indirectly affect the parent–child interaction or attachment time.

Table 1. The PPCT framework explaining bioecological factors affecting diabetes care and psychosocial functioning in children with diabetes mellitus

PPCT component	Diabetes care and psychosocial functioning issues
Process	Transactions between child with diabetes and immediate environment; e.g. low self-efficacy coupled with lack of family support affects glycaemic control
Person	Biological and genetic predispositions: alleles associated with T1DM, age, gender, weight and race are associated with diabetes care. Self-efficacy, motivation and personality traits affect and influence diabetes management. Co-morbid HIV and malaria complicate care
Context	
Microsystem	Home, school, peers' role in diabetes care and buffer psychosocial problems
Mesosystem	Interaction and effect of interaction on diabetes care and psychosocial well-being between parents and school, community health workers and child/family, church and counselling centre for psychological support
Exosystem	Parents' schedule, work stress/frustrations and how they affect diabetes care and child relationships
Macrosystem	Diabetes policies, budget for health, diabetes food and drug regulation, and cultural practices influence diabetes care
Time	Honeymoon period, the dawn phenomenon, adolescent period and counter-regulatory hormones, transition times, e.g. urbanisation and sedentary times

Finally, the fourth layer of the context is the macrosystem, which is a context encompassing any group (culture, subculture or other extended social structures) whose members share values or belief systems, resources, hazards, lifestyles, opportunity structures, life course options and patterns of social interchange.[10] An example of the macrosystem is an economic crisis in a country, which may shape the development of a child.

Time

The final element of the PPCT model is time. The time element of the model, also known as the chronosystem, includes components such as chronological age, and duration and nature of periodicity.[5] Time-related events such as a parent's debilitating illness, divorce or change of residence can have a more profound impact on a younger child compared to older ones.

Application of the bioecological model on diabetes care and psychosocial issues

'Nothing is as practical as a good theory' – Lewin Kurt, 1951: 169.[11] As with any robust theoretical model, Bronfenbrenner's ecological model of development is parsimonious and applicable to areas such as paediatric diabetes. The basic premise of the PPCT model of Bronfenbrenner's thinking is that health, behaviour and their determinants are interrelated.

Process

Paediatric diabetes takes place in a progressive and complex reciprocal interaction between an active, evolving child with diabetes and the people, objects and symbols in its immediate environment. Proximal processes are useful in clinical practice as tools to understand required adjustments to diabetes care and in understanding as well as adjusting the psychosocial well-being of children with diabetes. For instance, parental warmth and emotional availability are related to improved diabetes care and diabetes-related quality of life (QoL).[12]

The form, power, content and direction of proximal processes will affect diabetes care and psychological well-being based on the functions of the characteristics of the child.[6] For example, if the child has low self-efficacy and the people surrounding the child are not supportive of diabetes care, the child may have sub-optimal glycaemic control, especially in the absence of critical objects such as automatic insulin pumps.

An A_{1c} goal of < 7.5% (58 mmol/mol) is recommended across all paediatric age groups.[13] However, the increased use of basal–bolus regimens, insulin pumps, frequent blood glucose monitoring, goal setting and improved patient education in the youth from infancy to adolescence have been associated with more children reaching the blood glucose targets set by the American Diabetes Association in developed countries.[13-15] In developing countries, both proximal and distal processes make it difficult for children to reach the A_{1c} target of < 7.5% (58 mmol/mol).

From a diabetes care and psychosocial well-being inquiry perspective, examples of proximal processes, either protective or preventative, can be phrased in questions such as: Does the child get lessons about appropriate diabetes self-care activities? Does the child receive social support useful for diabetes management? Does the child get protection from physical and psychological harm, such as discrimination from other children? Does the child get nutrition suitable for diabetes management?

It is also important to note that children with diabetes are affected by distal processes including the family's own ability to support a child with diabetes as well as interact with other environments, of which the child is a part, for example, access to health centres or pharmacies for medical essentials, and resources to enable integration with people of different health status.

Person

The self of a child with diabetes is very important in determining levels of diabetes care and psychological well-being. The biological and genetic predisposition of the child have long been associated with diabetes mellitus,[16,17] diabetes care[18] and psychological well-being.[19] For the former, there are alleles or genetic variants associated with type 1 diabetes mellitus (T1DM), which either provide susceptibility or protection from acquiring the disease.[20] Further evidence for hereditary influence can be deduced from twin studies. The concordance for T1DM is approximately 50% for monozygotic twins and the risk to a first-degree relative is approximately 5%.[21]

Children with diabetes have personal characteristics that may affect diabetes care and their psychological well-being, such as their age, gender, weight and ethnicity. Firstly, insulin dose percentiles (ID-Perc) have been found to significantly differ during various periods of childhood and are influenced by gender, body weight and insulin injection regimes.[22] For instance, the 50th ID-Perc (P50) varied for insulin required for different ages: 0.67 IU/kg for age three years, 0.93 IU/kg for 13 years, and 0.70 IU/kg for 23 years, increasing from early childhood to adolescence and decreasing towards adulthood. The highest P50 ID was found at 12 years in females (0.94 IU/kg) and at 14 years in males (0.92 IU/kg).

In multivariate regression analysis, insulin dose was significantly ($p < 0.001$) associated with age, gender and insulin-delivery regime.[22] Moreover, one study found that children with diabetes were shorter (128.3 ± 24.3 vs 133.6 ± 24.7 cm) and lighter (29.2 ± 15.3 vs 31.3 ± 15.4 kg) than their peers without diabetes.[23] Height (–1.1 ± 1.2 vs –0.2 ± 0.8 m) and weight (–1.2 ± 1.3 vs –0.7 ± 1.3 kg) were also significantly lower in diabetic children compared to healthy controls ($p < 0.05$).[23]

Other studies indicate that the age of onset in South Africa and Ethiopia was later than elsewhere in the world,[24,25] and the peak age of onset of T1DM in sub-Saharan Africa was a decade later than in the West.[24,26,27] Ethnic differences in the peak age of onset have also been reported in some African countries. For instance, in South Africa, it has been reported that the peak age of onset was about 13 years in white South Africans (similar to Europeans) but about 23 years in black South Africans.[24] These ethnic differences may be due to socio-economic status and lifestyle differences between white and black people. There is also evidence that young people compared to adults have more challenges with diabetes self-care.[28]

Diabetes psychosocial issues tend to affect girls more than boys. A longitudinal study including 910 T1DM and 241 type 2 mellitus (T2DM) young people found that health-related quality of life (HRQL) for girls remained stable or decreased over time, whereas boys' HRQL increased.[29] Moreover, girls tended to report more depressive symptoms compared to boys.[30,31] Girls also tended to face more gender-specific discrimination and stigma related to diabetes than boys. For instance, girls with diabetes tend to be more perceived as reproductively unfit in romantic relationships than boys with diabetes, and also tended to have more worries concerning finding a romantic partner or the possibilities of giving birth.[32] These studies suggest that the impacts of diabetes on HRQL differ by gender and should be considered in clinical management.

Other personal characteristics useful for diabetes self-care are self-efficacy,[33] motivation[34] and personality traits.[35] Self-efficacy and motivation are useful in taking charge of one's own diabetes management. Personality can also be a barrier to or facilitator of support from others. Extroverts compared to introverts tend to have a wider social support network that may be useful for diabetes care.[36]

Physical maturity is one of the biggest challenges in diabetes management. The majority of T1DM is diagnosed in individuals younger than 18 years of age and this group requires unique aspects of care and management, such as adjusting insulin intake during this period of insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, and neurological vulnerability to hypo- and hyperglycaemia, as well as possible adverse neurocognitive effects of diabetes ketoacidosis.[13,37,38] In addition, some children with diabetes, especially in developing counties, have co-morbid conditions such as malaria,[39] HIV and AIDS,[40] and may also be undernourished due to high poverty levels, all of which complicate diabetes care and contribute to psychosocial problems.

Given the implications of the person with diabetes, considering personal characteristics of a child with diabetes in treatment choices, care and other interventions are crucial. Therefore, clinicians should

carefully consider predispositions of children with diabetes, such as age and gender, when deciding on a treatment plan. Psychological predisposition such as self-efficacy should be considered to optimise diabetes self-care and adherence to treatment.

Context

The environment or context in which a child with diabetes develops has implications for diabetes care and psychosocial well-being. The microsystem contains environments such as home, school or peer groups that have direct and indirect effects on diabetes care and psychosocial well-being. The home environment, especially family support and good home structure, is useful for diabetes care, in particular glucose monitoring. There is also a link between QoL and metabolic control, since poor metabolic control burdens the family.[41]

Diabetes can cause enormous pressure on how the family functions, which can either strengthen or break family ties, depending on the characteristics of a family.[32] During adolescence there is increasing independence and adolescents often challenge parents' supervision of their diabetes care. This may lead to conflicts within a family. T1DM is demanding and affects everyday lives of not only patients with diabetes but also their families and significant others. This may in turn exert stress on the family that is already burdened by diabetes management expenditure.

Diabetes-specific family conflict is related to poorer adherence and glycaemic control.[13] Advice given by parents or family members (e.g. 'Shouldn't you check your blood glucose? I think you are low!') can be perceived as offensive or intrusive behaviours in diabetes management, especially in adolescents who want to be or become independent.[32] On the other hand, constant respectful and unconditional support of patients' diabetes management may improve diabetes treatment outcomes.

In some cases, poor glycaemic control is because of lack of care-giver involvement, and poor or inconsistent family management and punitive or negative parenting. This is where healthcare providers should encourage developmentally appropriate family involvement in diabetes management tasks for children and adolescents, recognising that premature transfer of diabetes care to the child can result in non-adherence and deterioration in glycaemic control.[13]

In low-income homes, apportioning resources to household food stuffs can be a source of conflict, given that patients with diabetes are supposed to take certain diets that have low saturated fat composition and are rich in vegetables, part of a healthy diet, which may not be liked by other family members. This underscores the importance of family and friends in diabetes management.

Peers are useful in diabetes care. The literature suggests that friends' support for blood glucose testing is related to the patient's disease adaptation and QoL.[42] Peers can be supportive in diabetes care and can also thwart adaptation to the disease. Because adolescents with diabetes sometimes face discrimination from peers, they may want to hide the condition from others.[32] Some adolescents want to feel normal like their peers, which in turn makes them abandon their medical kits that often attract interest from their healthy peers, for fear of discrimination or unwanted attention.

Adolescents spend much of their time at school. Therefore, the school is an important agent for diabetes care and psychosocial well-being for children with diabetes. Despite the underscored importance of schools, children with diabetes in the school and day-care setting still face discrimination from teachers and the school system. Some schools may refuse admissions to children with diabetes and children in classrooms may not be provided with the assistance necessary to monitor glucose levels and may be prohibited from eating the necessary snacks.[13]

Sometimes the school may not know how to handle a child with a hypo- or hyperglycaemic episode. Therefore, each school should be acquainted with general guidelines for the care of a child with diabetes in the school and day-care setting, developed by various organisations such as the American Diabetes Association and national diabetes associations.[13] Broadly the guidelines include: (1) diabetes medical management plan, (2) responsibilities of various care providers, and (3) expectations of the student in diabetes care.[13]

The mesosystem from the diabetes perspective entails linkages and processes that influence diabetes care and psychosocial well-being in two or more settings containing the child with diabetes. This linkage of more settings can be exemplified by the recommendation from the American Diabetes Association that the parent/guardian should provide the school or day-care with materials and equipment necessary for diabetes care tasks, provide supplies to treat hypoglycaemia, and provide information about the student's meal/snack schedule and an emergency phone number for parent or guardian, among others.[13]

Diabetes-related stress in a family may contribute to poor glycaemic control. Given the developmental age of children, some may think the conflict is their fault due to their diabetes and may engage in self-destructive behaviour such as skipping injecting insulin or hospital appointments, or even resort to drastic measures such as suicide. This is when the relationship between community health workers, diabetes peer educators and family of the child with diabetes should be strengthened. This also includes encouraging the parent/guardian to accompany the child to hospital appointments in order to enable the heathcare provider to assess psychosocial issues in the family, which may affect diabetes care.

The connection between other larger structures such as church or community support groups can also be expected to have distal processes at work because they help the child and family cope with diabetes-related stress and get the necessary support for the child. Counselling services available to the family in times of need can influence the functioning of the mesosystem.[5]

The exosystem contains linkages and processes that indirectly influence processes within the immediate setting in which the developing child lives. For example, a parent's work schedule may influence the parent's involvement in diabetes care. In cases where a parent does not accompany a child to a hospital appointment, a common practice observed in Zambia,[19] the parent will have limited interaction with the healthcare provider, and for young children, they may perceive this as if they are unwanted by their parents.

In addition, parental work stress or frustrations from everyday household chores may in turn cause the parent to behave more irritably, which may make children think that it's their fault the parent is going through that anger and stress. Such perceptions may be the cause of drastic measures some children with diabetes sometimes go through, such as stopping taking medication or suicide attempts, to gain attention from the parents. Policies on how many appointments a child should attend at the hospital to receive certain services, for example, free insulin or syringes can all be considered as exosystem influences on the child.

The macrosystem contains the societal blueprint and influences the other systems mentioned above. Cultural beliefs and propensities

are some of those in the system that have an influence on diabetes care and psychosocial well-being. For instance, there are beliefs that girls with diabetes cannot give birth, and in developing countries, a good number of patients with diabetes consult traditional healers who claim to be able to cure diabetes.[32]

National health policies also influence diabetes care. Diabetes and obesity, for example, have social aetiological roots in the structure and lack of regulations on the food and tobacco industry, and the cultural tradition of a sedentary lifestyle. Santé diabètes, a non-governmental organisation working in the area of diabetes in Africa, points out that in recent years, there has been an overweight problem in Africa, especially with the sharp increase in the consumption of food that contains more saturated fat, and an increasing number of people with a sedentary lifestyle, as a result of rising income and urbanisation in Africa.[43] Urban lifestyle in Africa is characterised by changes in dietary habits involving an increase in consumption of refined sugars and saturated fat and a reduction in fibre intake.[44] These changes will probably further increase the risk of obesity and death.

Obesity in turn is particularly associated with an increased risk of developing T2DM. Moreover, sub-Saharan African consumers are increasingly aspiring to fast-food choices and most African countries such as Zambia, South Africa and Nigeria are among the top fast-food establishment destinations.[45] Consequently, urbanisation and its consequences on diabetes may increase the risk of stress and depression, which may compromise diabetes care. The development of stress and depression associated with urbanisation may also lead to the development of diabetes. The circle is a vicious one, which may also lead to other psychosocial problems such as increase in treatment costs, discrimination and poor QoL, among others.

Other macrosystem influences on diabetes include healthcare policies or guidelines such as the standards for diabetes medical care by the America Diabetes Association, which spell out how diabetes care should be effected.[13] Although in some countries, non-communicable disease policies and departments are in existence, their capacity to provide adequate medical care for persons with diabetes mellitus and also the prevention of T2DM is way below expected standards. For instance, in Zambia and Mozambique, referral pathways are poorly used and sometimes non-existent.[46] The Diabetes Foundation and International Insulin Foundation (IIF) found that three main problems were related to referrals in Zambia:

- lack of information given to users about their diagnosis in general and specifically about the reason for the referral
- many of the patients referred were not given a letter, which should have facilitated their entry into the hospital system
- lack of linkage from the hospital, back to the urban health centres for follow up.

A survey by IIF showed that healthcare workers where often (no figures reported) unfamiliar with the management of uncommon diseases such as diabetes. Diabetes was often mistaken for cerebral malaria; 21 out of 199 patients in Tanzania who were diagnosed as having cerebral malaria actually had diabetes mellitus.[46] To make matters worse, there is a lack of qualified human resources, essential medical drugs and poor access to health facilities, especially among rural clients. When medical drugs are available, they are expensive due to taxes and the procurement procedures.[47]

Budget allocations to healthcare, especially diabetes, are crucial determinants of the nature of care patients will receive. In 2009, the World Health Organisation reported that the 7.02 million cases of diabetes recorded by the WHO in African countries resulted in a total economic loss of US$ 25.51 billion, a figure which has since increased.[48] Political will and increased budget allocation to non-communicable diseases such as diabetes remain a challenge in most developing countries. Some countries such as Zambia subsidise the cost of medicines to make them accessible to patients. In addition, educational policies that encourage physical education can contribute to reducing the traditional sedentary lifestyle in children.

Time

A good example of how the chronosystem affects diabetes care and psychosocial well-being can be seen by examining the 'honeymoon' period. The honeymoon period is the time in people with T1DM shortly following diabetes diagnosis when the pancreas is still able to produce a significant amount of insulin to reduce insulin need and aid blood glucose control. Children with T1DM have often shown adjustment problems at the onset of diagnosis and after the honeymoon period is over.[49,50] Children find it difficult to adjust, especially injecting themselves with multiple insulin doses and adjusting their diet. This period is also when most adolescents experience stress related to diabetes care.[32]

The duration of diabetes from diagnosis plays a role in a child's psychological well-being. The developmental stage and physiological differences related to sexual maturity are crucial in deciding and implementing an optimal diabetes regimen plan.[13] In adolescents, non-adherence problems can be a result of the increase in counter-regulatory hormones (e.g. growth hormones, cortisol, epinephrine and glucagon) responsible for insulin resistance, a situation also known as the 'dawn phenomenon'.[51] This phenomenon is the night-to-morning elevation in blood glucose levels before and after breakfast in subjects with both T1DM and T2DM. In people without diabetes mellitus, blood glucose and plasma insulin concentrations remain remarkably flat and constant overnight, with a modest transient increase in insulin secretion just before dawn to restrain hepatic glucose production and prevent hyperglycaemia.[52] People without diabetes mellitus do not show symptoms of the dawn phenomenon.

Another issue worth discussing that occurs during the course of a person's development is the types of diabetes in relation to their age. The onset of T1DM can occur at any age, but is generally before the age of 40 years, while T2DM often has its onset after the age of 50 but can also develop before the age of 50 years.[2] However, due to demographic changes, people younger than 18 years old are now increasingly being diagnosed with T2DM.

The time component of Bronfenbrenner's model refers not only to chronological age and duration but also to the nature of periodicity. As alluded to earlier, in developing countries, changes in demographic characteristics and the rise of the middle class entails there will be a sharp increase in the consumption of food containing more saturated fat and an increasing number of people with a sedentary lifestyle.

Clinical and research implications

To begin with, clinicians and researchers should take into consideration the processes (proximal and distal), personal characteristics of the child with diabetes, micro-, meso-, exo- and macrosystems in which a child with diabetes lives and the chronosystem, and how these influence diabetes care and psychosocial well-being. Clinicians and

researchers should also know that two or more children may have equal resource characteristics and context, but their developmental trajectories will be quite different if one is motivated to succeed and persist in tasks despite having diabetes.

The child's well-being is linked to his or her resource characteristics, whether physical, mental or emotional, and the environment in which it exists. Therefore, assessment of the child's psychological well-being and environment are crucial in optimising diabetes care and psychosocial well-being of the child with diabetes.

To understand the lives of young people with diabetes, clinicians and researchers need to identify areas of strength and vulnerability in the child's ecology; understand the multi-directional interactions between nature and nurture and also that there is differential susceptibility to the influence of nature and nurture in children with diabetes; conduct evaluation studies to demonstrate efficacy of interventions targeting the ecology of a child with diabetes so that clinicians do not re-invent the wheel, undertaking interventions that do not work; and initiate and/or improve relationships between different stakeholders important for diabetes care such as the family, community, school, diabetes international bodies and pharmaceutical companies in order to improve the well-being of children. Then there is a need to sensitise and educate communities on diabetes and how to help children with diabetes so that positive outcomes for children are realised at the school and community level.

Conclusion

Deriving from empirical evidence, this article has illustrated how the bioecological model can be used to understand diabetes care and the psychosocial well-being of children. It shows that the proposition of ecological thinking is that diabetes, behaviour and its determinants are interrelated. Future studies should investigate how the bioecological model can be applied in everyday paediatric diabetes. This also means that ecological interventions that foster behavioural and contextual change through targeting environmental factors that are most likely to influence diabetes care and psychosocial well-being are possible. Unlike medical interventions delivered by a healthcare provider at the individual level, the proposed interventions are larger scale and emphasise the complexity of behaviour and the environment (person × environment interaction) rather than a person's behaviour only.

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Integrating the pieces of a complex puzzle to achieve a comprehensive approach towards optimal care of the patient with diabetes

S PILLAY, C ALDOUS

Abstract

Background: **Diabetes mellitus (DM) is ravaging both patients' health and healthcare economies of countries worldwide, especially in developing countries. Mitigation of the diabetes-related tsunami of complications could occur through optimal control of DM. Control of this disease begins at our local healthcare facilities and requires a comprehensive, standardised and holistic approach to care.**

Methods: **The diabetes clinic at Edendale Hospital is a busy regional clinic situated in Pietermaritzburg, KwaZulu-Natal. In order to improve diabetes care, the following integrated package of changes was made to this resource-limited clinic: (1) introduction of a fully operational multidisciplinary treatment team; (2) intensive nurse and clinician education on DM and its management according to local South African diabetes guidelines; (3) intensive patient education from all members of the team; (4) introduction of essential basic equipment into the clinic; (5) introduction of a patient clerking datasheet to ensure standardisation and comprehensive diabetes care for all patients visiting the clinic; and (6) development of a customised computer program to audit and analyse data over time in order to identify areas of poor performance within the care of the patient, and to monitor patient progress.**

Conclusion: **This article describes the development and implementation of the above six steps as a holistic patient-care package at the clinic. The overall management plan of diabetes care proposed within the clinic could provide the blueprint for other resource-limited diabetes clinics in developing countries.**

Introduction

Optimal control of diabetes mellitus (DM) ensures that the risk of micro- and macrovascular complications are minimised or prevented.[1] Aside from patient-related complications, especially cardiovascular, the economic burden of DM and its complications on the health economies of countries is enormous.[2,3] The latest International Diabetes Federation (IDF) estimates are that 77% of diabetic patients live in low- to middle-income countries and that approximately 62% of diabetic patients in Africa are undiagnosed.[4]

The diabetes pandemic in Africa is putting an enormous strain on a continent with limited resources and one that is already under strain from communicable diseases such as HIV infection and tuberculosis (TB). Coupled with the diabetes pandemic is obesity, which is increasing at an alarming rate worldwide. South Africa has the highest rates of obesity in females in sub-Saharan Africa, where approximately 42% of females and 39% of males are classified as obese.[5] Obesity is considered a risk factor for developing type 2 DM and is an important contributor to insulin resistance and poor glycaemic control.[6]

In South Africa, both in the private and state sectors, target glycaemic control is not being achieved.[7,8] Patient education is an essential first step towards diabetes control. This education process should be present at every level of the multidisciplinary team and is integral to achieving control.[9] The diabetes nurse-educator's role is pivotal in improving the quality of diabetes education imparted to patients.[10] Dietary advice to diabetic patients has shown benefit in improving glycaemic control.[11]

Patients with DM are about 20 times more likely to have lower-limb amputations compared with non-diabetics hence attention to foot care is paramount in their overall care.[12] Diabetic retinopathy accounts for the majority of cases of new onset of blindness in adults between 20 and 74 years of age.[13] Annual eye assessments form an essential component of optimal diabetes care. The risk of developing cardiovascular disease is two to three times higher in diabetic versus non-diabetic patients.[14] Routine electrocardiogram assessments may help in detecting silent myocardial ischaemia or infarctions among other abnormalities in diabetic patients.

DM is a chronic disease requiring the patient to take ownership of it. A fundamental aspect of self-control entails being able to manage diabetes at home. This requires self-monitoring of blood glucose levels (SMBG) by the patient. Guerci *et al.*[15] demonstrated that SMBG improves metabolic control in diabetic patients.

The Society for Endocrinology, Metabolism and Diabetes in South Africa (SEMDSA) 2012 diabetes guideline[16] provides direction for clinicians dealing with diabetic patients. Real benefits can be achieved by following these guidelines. However, studies have demonstrated that clinician compliance with these guidelines is still poor and control is sub-optimal.[7,17,18] Weingarten *et al.*,[19] in their meta-analysis of interventions in chronic diseases, showed that patient education and education of healthcare providers was associated with improvements in adherence to clinical guidelines by providers and resulted in definite improvements in patient disease control.

Organisational structural interventions within the clinic coupled with patient, nurse and clinician education has been shown to improve overall outcomes in diabetic patients.[20] One such intervention within

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the clinic is the introduction of electronic medical records (EMR). EMR serve important roles in ensuring more complete and accurate documentation by the clinicians working at the clinic, and secondarily help as a data-collection tool for research and auditing purposes.[21]

In this study we propose a model for a diabetes clinic, which addresses all of the above facets of DM patient care. This model can be applied to other resource-limited clinics in other developing world settings. We begin by describing the clinic at Edendale as it was (it is likely to be similar to many other diabetes clinics across the developing world), and then describe implementation of the multifaceted and holistic approach to patient care.

Optimal care of the diabetic patient, whether in resource-poor or well-resourced facilities, requires an integrated package of services geared towards holistic care of the patient. Fig. 1 is a diagrammatical representation of the steps implemented in the diabetes clinic, where each step of this process or 'piece of the puzzle' is interdependent on the other to ensure maximal effect on the outcomes of DM and its complications.

The clinic as it was

Before the implementation of the holistic integrated approach to diabetes care, the situation at Edendale diabetes clinic mirrored many in resource-poor areas. Edendale Hospital is a busy regional hospital situated in Pietermaritzburg, KwaZulu-Natal. Historically this resource-limited diabetes clinic had a poor booking system, which resulted in about 60 to 70 patients being consulted on one day per week.

Patients who were consulted had only their blood pressures (BP) taken and random blood glucose levels (RBG) determined prior to consulting one of the two doctors stationed at the diabetes clinic for the month. With such great numbers of patients and only two doctors in the clinic, most management decisions were made based on only the BP and RBG readings, with very little or no time spent on patient education or patient examination. Management decisions were made by the individual doctor at most times without any reference to local standardised diabetes guidelines. There was a lack of continuity of clinical care as these doctors were rotated on a monthly basis.

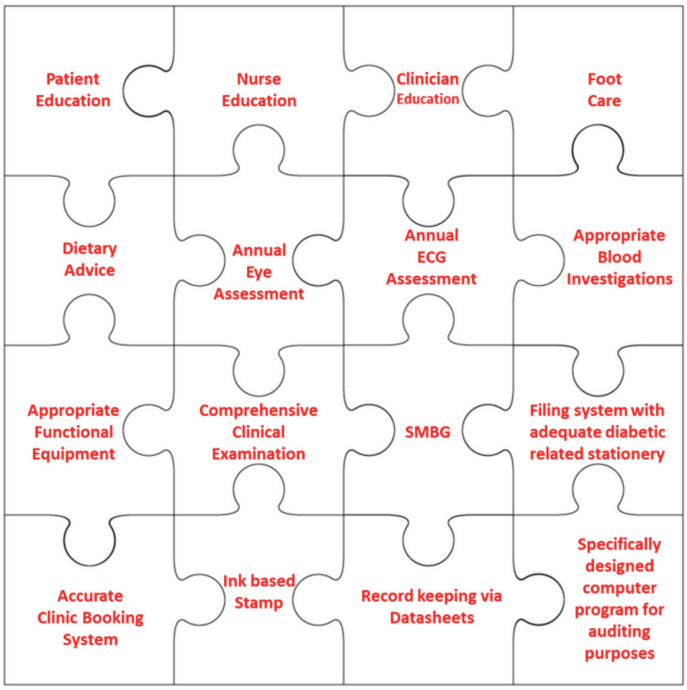


Fig. 1. Schematic representation of integrated elements of a comprehensive and holistic treatment approach to diabetic patients.

The clinic facility, being in a resource-limited environment, lacked adequate equipment for height, weight and waist measurements, and urine dipsticks were only performed if patients presented to the clinic with an RBG > 20 mmol/l, and then looking for ketonuria only. The two rooms used for this busy clinic run on Wednesdays were used for other clinics for the rest of the week. The correct stationery/forms specific to diabetes care were therefore always in short supply and, if present, difficult to locate. No tuning forks, patellar hammers or monofilament testing equipment were available at the clinic. The wall-mounted ophthalmoscopes in both rooms were non-functional.

This description of the clinic probably reflects a typical diabetes clinic service run in most similar hospitals in the country.

Changes implemented

Having assessed the diabetes clinic in this resource-limited hospital, the following changes were introduced in an integrated manner to improve overall diabetes care.

Physical facilities

Three rooms for the running of the diabetes clinic were allocated and clearly labelled for dedicated use. Being permanently allocated for this purpose, they could be equipped and locked when not in use.

Equipment

Equipment such as tuning forks, patellar hammers, monofilaments and a body mass index (BMI) scale was donated for use in the clinic. New ophthalmoscopes were provided.

Patient education

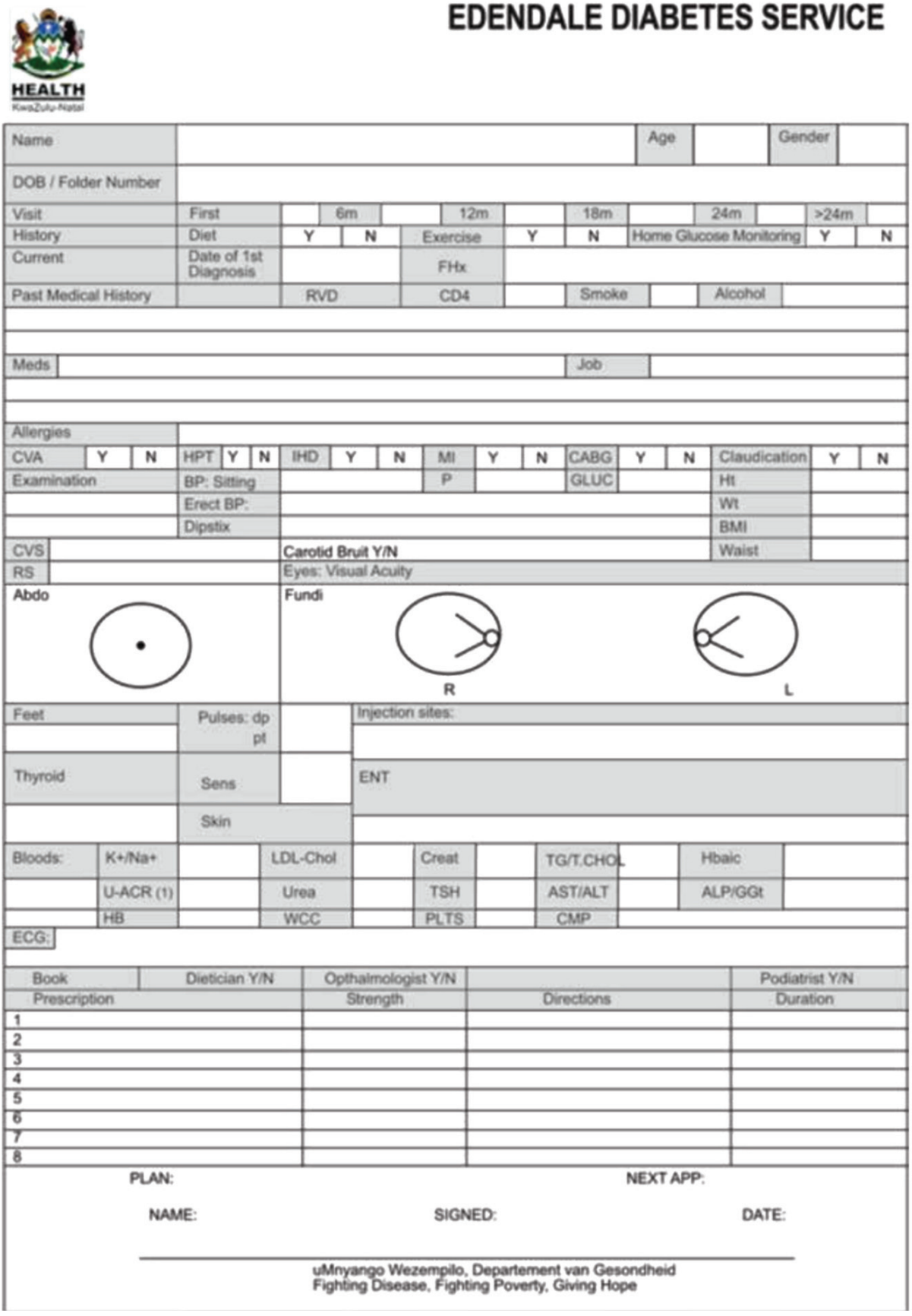
Patient education material in the form of posters was acquired and displayed for easy patient reading while waiting. A diabetes nurse-educator was employed and stationed at the clinic. In conjunction with the sessional family physician, patient education sessions are conducted while patients wait for their vital signs to be recorded.

Staffing

A multidisciplinary clinical team was set up to address all aspects of diabetes care and includes the following members: specialist physician, family physician, medical officers, interns, nursing staff, diabetes nurse-educator, dieticians, podiatrist, and ophthalmologist for annual review. All members of this team other than the ophthalmologist are present at the weekly clinics to deliver their specialised care.

Patients waiting for consultation are allocated to the next clinician available –the intern, medical officer, family or specialist physician. Junior clinicians have immediate access to senior doctors working in the clinic to discuss their patients and issues relating to their management. Patients who need to consult podiatrists are identified by the clinicians and then referred accordingly.

A podiatrist plays an integral part in the prevention and management of diabetic foot complications.[22] After consultation with the podiatrist, employed by the local tertiary hospital, it was agreed that she would consult diabetic patients and also provide weekly group diabetic foot-care education at the clinic.



HEALTH
KwaZulu-Natal

EDENDALE DIABETES SERVICE

Name														Age		Gender			
DOB / Folder Number																			
Visit	First		6m		12m		18m		24m		>24m								
History	Diet	Y	N	Exercise	Y	N	Home Glucose Monitoring	Y	N										
Current	Date of 1st Diagnosis			FHx															
Past Medical History		RVD		CD4		Smoke		Alcohol											
Meds								Job											
Allergies																			
CVA	Y	N	HPT	Y	N	IHD	Y	N	MI	Y	N	CABG	Y	N	Claudication	Y	N		
Examination	BP: Sitting				P			GLUC			Ht								
	Erect BP:										Wt								
	Dipstix										BMI								
CVS		Carotid Bruit Y/N									Waist								
RS		Eyes: Visual Acuity																	
Abdo		Fundi																	
		R																	
		L																	
Feet		Pulses: dp pt		Injection sites:															
Thyroid		Sens		ENT															
		Skin																	
Bloods:	K+/Na+		LDL-Chol		Creat		TG/T.CHOL		Hbaic										
	U-ACR (1)		Urea		TSH		AST/ALT		ALP/GGt										
	HB		WCC		PLTS		CMP												
ECG:																			

Book	Dietician Y/N	Opthalmologist Y/N		Podiatrist Y/N
Prescription		Strength	Directions	Duration
1				
2				
3				
4				
5				
6				
7				
8				

PLAN: NEXT APP:

NAME: SIGNED: DATE:

uMnyango Wezempilo, Departement van Gesondheid
Fighting Disease, Fighting Poverty, Giving Hope

Fig. 2. The comprehensive diabetes datasheet.

Following consultation with the dietetics department at Edendale Hospital, it was agreed that all clinic patients were to be consulted annually at a minimum. Diabetes dietary guidelines are distributed for the different language groups. Dieticians come to the clinic weekly and provide group patient education.

The above multidisciplinary team provide holistic management of DM. Having more doctors available at the clinic aimed to ensure that doctors had more time available to spend consulting and educating patients.

Staff training

Nursing staff working at the clinic were trained on all aspects of diabetes care by the specialist clinicians employed at the clinic.

Clinic management

An appointment system was introduced, which was controlled by the diabetes nurse educator. The number of patients seen per week is limited to a manageable number, between 30 and 40. Previously, the large number of clinic patients included mostly stable diabetic patients who could have been down-referred to their local clinics. Once proper referral and inclusion from and into the clinic was achieved, the number of patients seen at the clinic was maintained at between 30 and 40 per week. A filing system was introduced where all forms pertaining to diabetes care were kept and replenished when necessary.

Clinical examination

Computer and printing facilities are scarce in resource-poor clinics. To address the need for standard data collection in the out-patient (OP) file, an ink stamp was designed, which creates a form for collection of relevant data. This stamp includes the following clinical fields that need to be filled in by the nursing staff:

- sitting and standing BPs as described in the 2011 South African hypertension guideline[23]
- resting pulse rate (beats per minute)
- height (cm)
- weight (kg)
- BMI (kg/m^2)
- waist circumference (cm)
- urine dipsticks, now routinely performed on all patients attending the clinic and looking for all variables, not restricted to ketonuria only
- RBG (mmol/l).

Together with nurse training, this ink-based stamp, which created a page with spaces for all the standard vital readings to be recorded, ensures that nursing staff perform standardised examinations for all patients and that they document details in the OP folder.

A comprehensive diabetes datasheet (hereafter referred to as the datasheet) was designed and implemented (Fig. 2). This datasheet is completed in triplicate so that one copy is fixed to the OP file and another copy given to the patient with the explicit instruction that the patient should present this datasheet if he/she consults another healthcare profession or institution; the intention was dissemination of correct patient medical history and management. The third copy is kept at the clinic and used for data capturing.

The datasheet ensures that all patients are consulted and managed in a comprehensive and standardised way, and no areas of clinical assessment and examination are omitted by the attending clinician. The principle of the datasheet is based on a comprehensive diabetes approach where the following aspects need to be covered:

- patient medical history, including history of retroviral disease
- assessment of lifestyle issues in respect of compliance with a diabetes diet, exercise regimen, smoking and ethanol consumption
- performing of SMBG.

The following section of the datasheet requires the patient's vital details to be assessed from the OP file. These have already been completed by nursing staff but need to be transcribed from the OP file onto the datasheet by the attending clinician, thus ensuring that the clinician assesses this important part of the examination. The act of transcribing ensures cognisance is taken of the readings by the clinician.

Thereafter the clinician's full diabetes physical examination needs to be entered onto the datasheet. All clinicians working at the diabetes clinic are trained on how to perform a comprehensive diabetes clinical examination and manage patients according to the local SEMDSA diabetes guideline of 2012.[16] Laminated copies of the 2012 SEMDSA diabetes guideline are fixed to the walls of each of the three consulting rooms for ease of reference.

Integral to the function of the datasheet is the reminder to clinicians (via tick boxes) of the need for regular ophthalmological, blood, podiatry, dietician and electrocardiogram (ECG) assessments. These areas are often forgotten and patients suffer as a result, in the form of poor control and complications. Previous blood results are required to be entered on the datasheet, ensuring that the clinician retrieves and reviews these results.

At the bottom of the datasheet, the patient's complete list of medications prescribed is entered. This serves an important role, to allow the dissemination of patient information to their local health clinics and private doctors if need be.

Records management

A computer program was designed to correspond to the datasheet, allowing capture of all variables from the datasheet onto the program. This program was written using Visual Basic. net and .net technologies. The program uses the date of birth (DOB) as the identifier for each patient record. If two patients have the same DOB then the program automatically assigns a numerical value after the DOB (i.e. two patients with DOB of 720511 would then be recorded as 720511 for first patient and 720511_1 for next patient and so on). Name and gender requires alphabetical entries while age needs a numerical entry. The following entries require alphabetical data boxes (Yes/No) to be completed:

- diet
- exercise
- home glucose monitoring
- smoking
- alcohol
- cerebrovascular accident
- hypertension
- ischaemic heart disease
- myocardial infarction
- coronary artery bypass graft
- intermittent claudication
- carotid bruit
- family history of DM
- retroviral status.

The purpose of having data boxes in the program was for ease of use and to speed up the process of data capturing. Numerical data entries are needed for the following:

- year of first diagnosis of DM
- cluster of differentiation (CD4) count
- sitting and erect BP
- resting pulse rate
- RBG
- height/weight/BMI/waist circumference.

A second page in the program was created to allow the user to capture blood results with the date that the blood is drawn. The purpose of entering dates for each set of blood results is that the initial blood results can be used as a baseline with which to compare future results. The program allows the user to enter multiple blood results that are found in the file, each with its own date. This allows collection of a complete history of patients' blood results. Blood results that cannot be found in the patient's chart are traced on the National Health Laboratory Service (NHLS) website.

For eye assessments, the program was designed to allow the user to choose Yes/No for the following:

- glaucoma
- cataracts
- proliferative retinopathy
- non-proliferative retinopathy.

If the user entered 'Yes' to any one or more of the above for eye assessment, the program then enquired whether it was right, left or bilateral.

Once again a separate page in the program was created for ECG analyses. The following is required for every ECG:

- axis: data box options under this include right, left or normal
- ventricular hypertrophy: data box options include right, left and none
- bundle branch block (BBB): data box options here include RBBB, LBBB, left anterior fascicular block, left posterior fascicular block, bifasicicular block, none
- evidence of previous MI: if 'Yes', then the following boxes will open:
  - inferior territory MI
  - anterior territory MI
  - lateral territory MI
  - anterolateral territory MI
  - none.

The program was designed to interpret and group the various leads into inferior, anterior, lateral or anterolateral territories.

- premature ventricular contractions: data box for Yes/No
- atrial fibrillation or atrial flutter: data box for Yes/No
- T-wave abnormalities: if 'Yes', data box for T-wave inversion or peak T-waves.

Another tab was created for urine dipstick results and includes the following parameters:

- date of dipstick
- Yes/No boxes present for each of the following parameters:
  - red blood cells
  - white blood cells
  - protein
  - ketones
  - glycosuria.

If any of the above boxes are marked as 'Yes' then the program offers the user a range from 1+ to 4+ as tick boxes to enter the quantity.

For evidence of clinical neuropathy, there are data boxes for sensory and motor neuropathy. For thyroid examination data, there are boxes for normal and goitre. For injection site data the user has choices of normal, lipoatrophy, lipodystrophy or cellulitis.

With regard to drug prescription, a comprehensive list of commonly prescribed medications was compiled and captured. The program gives the user a chance to view the list of medications alphabetically or use the search function to retrieve the medication, then to choose the drug and add the dosage (if different from the dosage already stored on the program). It was recognised that the program might not list all medications so it was modified to allow the user to capture a new drug that is not on this list. The program was designed to allow the user to add to this list of medications and save these new drugs for future reference.

For data analysis purposes, the programmer was commissioned to program the various comparisons required for patient and clinic monitoring and reports were generated by Crystal® reports [SAP SE (Systems, Applications & Products in Data Processing) Germany]. The comparisons required were decided on based on clinical requirement for auditing.

In the main menu of the program, an option tab exists for reports, and within this section various reports are available for review purposes. Some examples include reports comparing the type of DM with mean glycosylated haemoglobin achieved, and reports comparing the number of patients with type 1 and type 2 DM.

Discussion

This integrated approach to DM management within this resource-limited clinic ensures that all patients consulted at the clinic are evaluated and managed in a structured and comprehensive way. DM is a non-communicable disease with devastating complications if uncontrolled. Complications can be reduced with adequate control.[1] Local guidelines provide a structured approach to diabetes management; however, very few clinicians actually follow these guidelines and this may be one of the reasons why so few patients achieve targeted control of their disease.

We believe that introducing a multifaceted approach targeting both the clinician and patient will help improve control in this regional-level diabetes clinic. The booking system ensures that the numbers of patients seen at the clinic is regulated (decreased from 60–70 to 30–40 patients per week). Together with the additional doctors working at the clinic, this means that patients are now spending more quality consulting time with the clinician. Initially patients were apprehensive of the longer consultation times and consulting the various members of the team. However, they soon realised that the overall benefits they gained outweighed their increased consulting times.

Patients get the benefit of a fully operational multidisciplinary team, which includes nursing staff, dieticians, podiatrist, family and specialist physicians, interns and medical officers. Patient education is provided by every member of this team. Nursing staff are trained in weekly special sessions on diabetes care and management. All clinicians, prior to working in the clinic, are also trained on diabetes management using the 2012 SEMDSA guideline. A datasheet was developed and introduced into the clinic. This datasheet ensures that all diabetic patients receive a standardised and comprehensive assessment and management that follows local diabetes guidelines. It also ensures that commonly

forgotten areas of diabetes management (such as podiatry and annual eye assessments, among others) are reinforced.

Having data captured onto a specifically designed program enables us to first assess the baseline state of control in the clinic and then monitor changes in control in subsequent years. The results of such comparisons will help us to objectively make any further improvements as required. The initial study conducted by Pillay *et al.* demonstrated sub-optimal diabetes control within this diabetes clinic.[8] The overall diabetes control has improved significantly since the multifaceted approach was fully incorporated into the clinic.[24]

Conclusion

Diabetes care in this resource-limited clinic was inadequate, with large numbers of patients consulted by only a few rotating doctors. This scenario has now improved to include a multidisciplinary team (including increased numbers of doctors) coupled with a comprehensive and standardised approach to all patients consulted at this clinic. Based on the promising clinical outcomes shown by Pillay *et al.* in this clinic post implementation of the multifaceted approach, this model could serve as a possible blueprint and could easily be adapted to other clinics, and district and regional hospitals in the country.[24] Data sheets could be completed in other regional or district hospital diabetes clinics in the province and sent to the central regional hospital for capturing into this specialised computer program. This process will provide extensive information on diabetic patients and their control within the province. Control of this 'diabetes puzzle' need not be an insurmountable task if a multifaceted approach is attempted.

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Effects of a PPAR-gamma receptor agonist and an angiotensin receptor antagonist on aortic contractile responses to alpha receptor agonists in diabetic and/or hypertensive rats

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Abstract

Aim: **The aim of this study was to investigate the effects of pioglitazone and losartan pre-treatment on the aortic contractile response to the alpha-1 agonist, phenylephrine, and the alpha-2 agonist, clonidine, in L-NAME-induced hypertensive, STZ-induced diabetic, and hypertensive diabetic rats.**

Methods: **Male Wistar rats were randomly allocated to four groups: control, diabetic (DM), hypertensive (HT) and hypertensive diabetic (HT + DM) groups. Three weeks after drug application, *in vitro* dose–response curves to phenylephrine (Phe) (10-9–10-5 M) and clonidine (Clo) (10-9–10-5 M) were recorded in aortic rings in the absence (control) and presence of pioglitazone (10 µM) and/or losartan (10 µM).**

Results: **Pioglitazone and losartan caused a shift to the right in contractile response to phenylephrine in all groups. The sensitivity of the aortic rings to phenylephrine was decreased in the presence of pioglitazone and/or losartan in all groups. The contractile response of clonidine decreased in the presence of pioglitazone and/or losartan in the control, HT and DM groups.**

Conclusion: **The sensitivity of aortic rings to alpha-1 and alpha-2 adrenoceptors was decreased in the presence of pioglitazone and/or losartan in diabetic and hypertensive rats. Concomitant use of PPAR-gamma agonists, thiazolidinediones, and angiotensin receptor blockers may be effective treatment for diabetes and hypertension.**

Keywords: diabetes, hypertension, pioglitazone, losartan, alpha adrenoceptors

Hypertension and diabetes mellitus are both common diseases worldwide and they co-exist frequently, resulting in significant rates of morbidity and mortality. Diabetes mellitus and hypertension have been identified as risk factors for cardiovascular disease and cause altered vascular responsiveness to several vasoconstrictors and vasodilators.[1-3] Endothelium-dependent vasodilation is reduced in diabetes, largely due to excessive oxidative stress and the bio-availability of nitric oxide. Endothelium-derived nitric oxide (NO) is a potent endogenous nitrovasodilator and plays a major role in modulation of vascular tone.[4] NG-nitro-L-arginine methyl ester (L-NAME)- induced hypertension has been one of the most frequently used models of experimental hypertension since 1990.[5]

Thiazolidinediones (TZDs) such as pioglitazone are a class of oral antidiabetic agent that act primarily by decreasing insulin resistance. Drugs in this class act as potent and highly selective agonists for peroxisome proliferator-activated receptor gamma (PPARg).[6] Pioglitazone repairs blunted endothelium-dependent vasodilatation, protects against oxidative stress and lowers blood pressure.[7-11] The vascular endothelium mediates relaxant responses to a wide range of vasodilators and modulates the constrictor responses to alpha agonists such as phenylephrine and clonidine.

The streptozotocin (STZ)-induced diabetic rat model has been widely used to study changes in vascular reactivity to alpha adrenoceptor agonists.[12] Hyperglycaemia is likely to modulate physiological responses to angiotensin II and may contribute to the pathogenesis of vascular dysfunction in diabetes.[13] Angiotensin type 1 receptor (AT1R) blockers (ARBs) such as losartan are widely used in the treatment of hypertension.[14,15]

It is not clear how concomitant use of medication in the treatment of hypertension and diabetes has effects on vascular contractility. Hence the aim of this study was to investigate the effect of pioglitazone and losartan pre-treatment on the aortic contractile response to the alpha-1 agonist, phenylephrine (Phe), and the alpha-2 agonist, clonidine (Clo), in L-NAME-induced hypertensive, STZ-induced diabetic, and hypertensive diabetic rats.

Methods

Male Wistar rats (250–300 g) were obtained from the experimental animal centre of Adnan Menderes University and all experiments were performed according to the principles and guidelines of the Adnan Menderes University animal ethics committee. Male Wistar rats were randomly allocated to four groups: a control group (Cont) (n = 15), a diabetic group (DM) (n = 20), a hypertensive group (HT) (n = 20), and a hypertensive diabetic group (HT + DM) (n = 20).

All rats were housed at 22–24°C on a 12-hour dark–light cycle and received food and water (or L-NAME solution in drinking water in the hypertensive groups) ad libitum. Diabetes was induced by a

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single intraperitoneal injection of 50 mg/kg STZ in the DM group. Hypertension was induced by giving L-NAME (50 mg/kg) in the drinking water for three weeks in the HT group. Hypertension plus diabetes were induced by a single intraperitoneal injection of 50 mg/kg STZ and providing L-NAME (50 mg/kg) in the drinking water for three weeks in the HT + DM group.

Body weights of the treated groups were measured at weekly intervals. *In vitro* experiments were started three weeks after the drug injections. Systolic blood pressure (SBP) of the rats was measured before the *in vitro* experiments using the tail-cuff method. Blood was obtained from a tail vein in conscious rats. At least five readings were done at every session and the mean of four values was used to obtain the SBP of each rat. Glucose concentrations were determined using an International Medical Equipment Diabetes Care (IME-DC) blood glucose meter (Oberkotzau, Germany).

Preparation of aortic rings and in vitro experiments

The rats were anaesthetised with ketamine and xylasine (50 and 5 mg/kg intraperitoneal, respectively). A thoracotomy was performed and the thoracic aorta was removed from the diaphragm to the heart. The aorta was then placed in ice-cold Krebs' solution where it was cleaned and any adhering fat was removed. The composition of the Krebs' solution (mmol/l) was 118.0 NaCl; 25.0 $NaHCO_3$; 4.7 KCl; 1.2 KH_2PO_4; 1.2 $MgSO_4 \cdot 7H_2O$; 2.5 $CaCl_2$; and 10.1 glucose.

The aorta was then cut into small rings (4–5 mm in width). The rings were suspended horizontally between two stainless steel wires and mounted in a 20-ml organ bath filled with warmed (37°C) and oxygenated (95% O_2 and 5% CO_2) Krebs' solution. One end of the ring was connected to a force transducer (MAY FDT 05, Commat Ltd. Ankara, Turkey). The rings were equilibrated for 60 min under a resting tension of 2 g with the bath fluids being changed every 15 min. Measurement of the isometric force was recorded on a data-acquisition system (MP 36, Biopac Systems, Inc).

After the equilibration period, the rings were sub-maximally contracted with Phe (10-7 M), and the cumulative concentration–response curve to acetylcholine (10-9–10-5 M) was then obtained to test their contractile capacity. Intact vessels failing to achieve at least 60% relaxation to acetylcholine were assumed to be damaged and were discarded. Cumulative responses to Phe (10-9–10-5 M) and Clo (10-9–10-5 M) were recorded in the aortic rings in the absence (control) and presence of pioglitazone (10 µM) and/or losartan (10 µM), which was added to the bathing solution 15 min prior to the contractile responses of Phe or Clo.

Pioglitazone hydrochloride was obtained as a gift sample from Sandoz (Istanbul, Turkey). Streptozotocin, phenylephrine, clonidine, L-NAME and the other chemicals were purchased from Sigma Chemicals. Losartan potassium was purchased from Fluka China (Interlab, Izmir, Turkey).

Statistical analysis

The results are expressed as mean ± SEM. Statistical evaluation of the data was performed by analysis of variance (ANOVA) and the Student's *t*-test. Results were considered significant when $p < 0.05$. The agonist pD_2 value (–log EC50) was calculated from the concentration–response curve by non-linear regression analysis of the curve, using a base-fitting program (Prism, Graphpad).

Results

STZ-injected animals developed diabetes in the DM and HT + DM groups. In the HT + DM group, five rats died in the first week after the STZ injection. The body weights, blood glucose levels and SBP are shown in Table 1.

There was a significant increase in blood glucose levels in the STZ-injected groups (DM and HT + DM groups). The daily intake of L-NAME was calculated from the daily water intake and was approximately 21–23 mg/kg/day for the HT and HT + DM groups. There was a significant increase in SBP in the L-NAME-treated groups (HT and HT + DM groups) (Table 1).

Phe induced a concentration-dependent contractile response in the aortic rings from all four groups. These curves are shown in Figs 1–4. There was no significant change in maximum contractile response (E_{max}) to Phe in all groups due to the presence of pioglitazone and/or losartan; these drugs shifted the contractile response to Phe to the right. The sensitivity of the aortic rings to Phe was however decreased in the presence of pioglitazone and/or losartan in all groups [Table 2 (pD_2 value)].

There was significant decrease in maximum contractile response (Emax) to Clo in the control group due to the presence of pioglitazone and/or losartan (Fig 5). In the absence of pioglitazone and losartan (control), Clo induced contraction. In the presence of

Table 1. Body weight, blood glucose levels and systolic blood pressure before the in vitro experiments

Parameters	Control group (n = 15)	DM group (n = 20)	HT group (n = 20)	HT+DM group (n = 15)
Body weight (g)	275.1 ± 6.1	279.1 ± 5.9	309.4 ± 9.5	201.1 ± 7.2[a]
Blood glucose level (mg/dl)	120.3 ± 6.6	371.7 ± 18.1[b]	177.6 ± 15.4	395.4 ± 14.1[b]
Systolic blood pressure (mmHg)	96.4 ± 2.9	155.2 ± 5.2[c]	187.9 ± 3.9[c]	161.5 ± 7.1[c]

Values are expressed as mean ± SEM.
[a]$p < 0.05$, compared to control group.
[b]$p < 0.05$, compared to control group. Blood glucose levels > 250 mg/dl (13.88 mmol/l) indicated diabetes.
[c]$p < 0.05$, compared to control group.

Table 2. Acute effects of pioglitazone and losartan on vascular sensitivity (pD2) to pheylephrine in segments of thoracic aorta from Wistar rats

	Control group pD_2 (n = 15)	HT group pD_2 (n = 7)	DM group pD_2 (n = 19)	HT+DM group pD_2 (n = 12)
Control	7.26 ± 0.08	7.53 ± 0.04	7.29 ± 0.07	7.27 ± 0.07
Pioglitazone	6.80 ± 0.08[a]	7.04 ± 0.07[a]	7.10 ± 0.06[a]	7.23 ± 0.07
Losartan	6.76 ± 0.10[b]	6.95 ± 0.13[b]	7.03 ± 0.06[b]	7.13 ± 0.10
Pioglitazone + losartan	6.61 ± 0.08[c]	6.81 ± 0.08[c,d]	6.97 ± 0.05[c]	6.97 ± 0.09[c,d]

n is the number of aortic segments in each group. Values are expressed as mean ± SEM.
Cont: control, Pio: pioglitazone, Los: losartan, Pio+Los: pioglitazone + losartan.
Control group: [a]Cont vs pio ($p < 0.001$); [b]Cont vs los ($p < 0.001$); [c]Cont vs pio+los ($p < 0.001$).
HT group: [a]Cont vs pio ($p < 0.001$); [b]Cont vs los ($p < 0.001$); [c]Cont vs pio+los ($p < 0.001$); [d]Pio vs pio+los ($p = 0.046$).
DM group: [a]Cont vs pio ($p = 0.037$); [b]Cont vs los ($p = 0.005$); [c]Cont vs pio+los ($p = 0.001$).
HT + DM group: [c]Cont vs pio+los ($p = 0.013$); [d]Pio vs pio+los ($p = 0.030$).

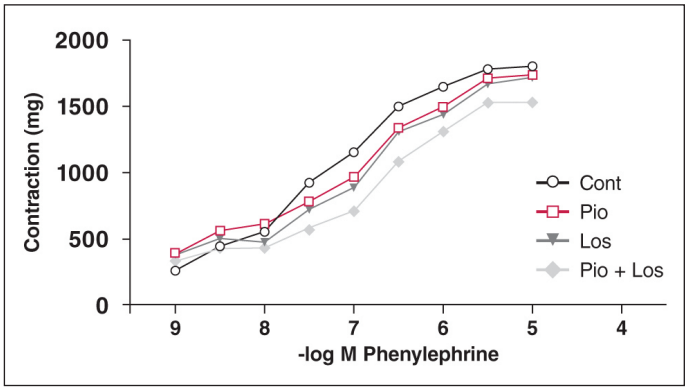

Figure 1. Effects of pioglitazone and losartan on the response of aortic segments to increasing concentrations of phenylephrine in the control group. Cont: control, Pio: pioglitazone, Los: losartan, Pio+Los: pioglitazone + losartan. Values are expressed as mean ± SEM.

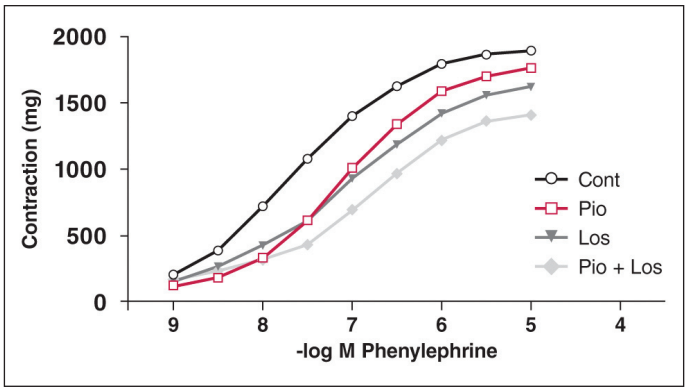

Figure 2. Effects of pioglitazone and losartan on the response of aortic segments to increasing concentrations of phenylephrine in the HT group. Cont: control, Pio: pioglitazone, Los: losartan, Pio+Los: pioglitazone + losartan. Values are expressed as mean ± SEM.

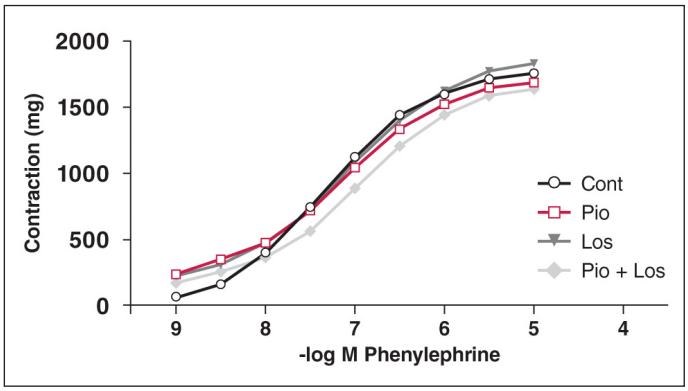

Figure 3. Effects of pioglitazone and losartan on the response of aortic segments to increasing concentrations of phenylephrine in DM group. Cont: control, Pio: pioglitazone, Los: losartan, Pio+Los: pioglitazone + losartan. Values are expressed as mean ± SEM.

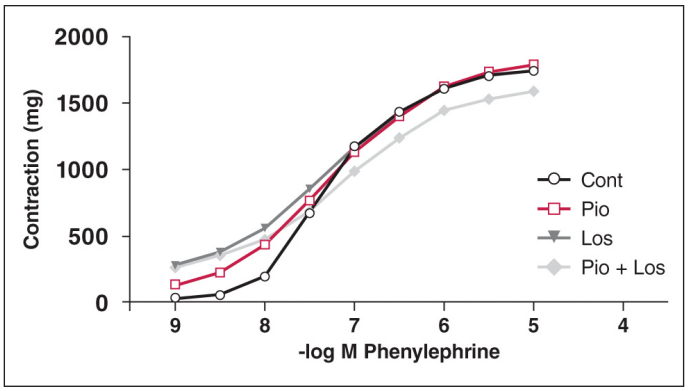

Figure 4. Effects of pioglitazone and losartan on the response of aortic segments to increasing concentrations of phenylephrine in the HT + DM group. Cont: control, Pio: pioglitazone, Los : losartan, Pio+Los: pioglitazone + losartan. Values are expressed as mean ± SEM.

pioglitazone and/or losartan, Clo induced relaxation in the control aortic rings (Fig. 5).

In the HT group, Clo did not cause relaxation. The contractile response to Clo was decreased in the presence of pioglitazone and/or losartan (Fig. 6). In the DM group, the contractile response to Clo was significantly decreased in the presence of pioglitazone and losartan, but not in the presence of either pioglitazone or losartan alone (Fig. 7). In the HT + DM group, the decrease in contractile response to Clo was not significant in the presence of pioglitazone and losartan (Fig. 8).

Discussion

This study investigated the effects of pioglitazone and losartan on aortic contractile responses to alpha adrenoceptors in diabetic and/or hypertensive rats. We examined the effects of pioglitazone and losartan on vascular contractility in control, L-NAME-induced hypertensive, STZ-induced diabetic, and hypertensive diabetic rats. The major findings of this study were that pre-treatment of rat aortic rings with pioglitazone (10 μM) and/or losartan (10 μM) decreased the sensitivity of the contractile responses to phenylephrine and decreased the maximum clonidine contraction.

Various authors have reported on the blood pressure- lowering effects of PPAR-gamma agonists such as pioglitazone in rats and monkeys, and in patients with type 2 diabetes and hypertension.[9,16-18] Majithiya *et al*. noted an increase in SBP in STZ-induced (55 mg/kg, intravenous) diabetic Sprague-Dawley rats, and also reported that pioglitazone administration to these rats lowered their blood pressure.[10] Diep *et al*. showed that treatment with pioglitazone (10 mg/kg/day) or rosiglitazone (5 mg/kg/day) for seven days attenuated the development of hypertension, improved endothelial dysfunction induced by angiotensin II infusion, and corrected vascular structural abnormalities.[19]

Nomura and co-workers reported their findings regarding the effect of pioglitazone on the contractility of isolated blood vessels.[20] Buchanan and colleagues showed that the addition of pioglitazone to vascular preparations decreased KCl- and norepinephrine-induced vasoconstriction *in vitro*.[11] Accordng to Majithiya and co-workers, administration of pioglitazone for four weeks restored elevated blood pressure to normal, reduced the enhanced contractility to phenylephrine, and restored acetyl choline-induced relaxation.[10]

The endothelium is involved in the beneficial vascular action of the glitazones.[21] Various authors have shown that pioglitazone directly dilates blood vessels by blocking the calcium channels.[11,22] It has been reported that a decrease in blood pressure due to pioglitazone is due to direct dilation of the vascular smooth muscles by blocking the calcium channels or reducing total peripheral resistance.[11,22,23]

In vivo PPAR-alpha and -gamma agonists have been shown to reduce superoxide generation, restore endothelial dysfunction and

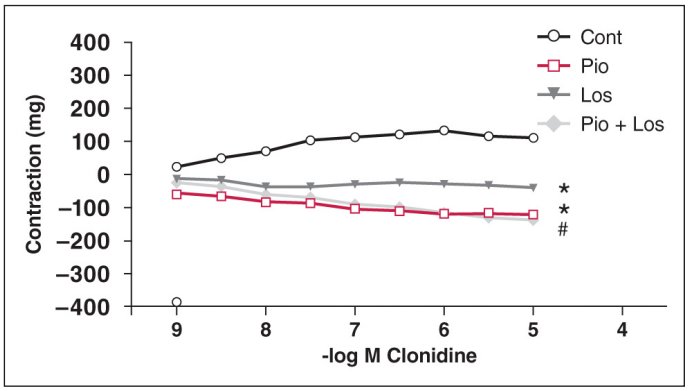

Figure 5. Effects of pioglitazone and losartan on the response of aortic segments to increasing concentrations of clonidine in the control group. Cont: control, Pio: pioglitazone, Los: losartan, Pio+Los: pioglitazone + losartan. Values are expressed as mean ± SEM (n = 14). *Cont vs Pio (p = 0.001); *Cont vs Los (p = 0.011); #Cont vs Pio+Los (p < 0.001).

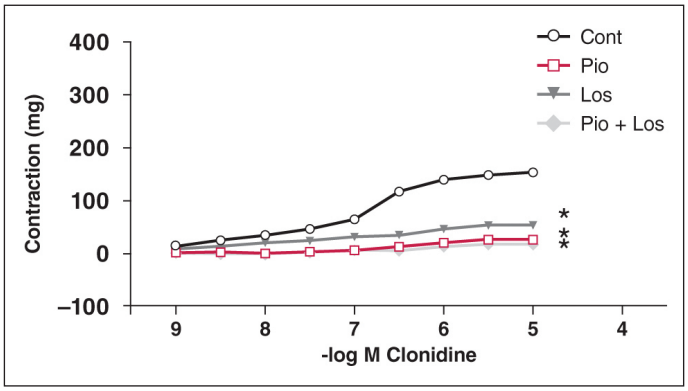

Figure 6. Effects of pioglitazone and losartan on the response of aortic segments to increasing concentrations of clonidine in the HT group. Cont: control, Pio: pioglitazone, Los: losartan, Pio+Los: pioglitazone + losartan. Values are expressed as mean ± SEM (n = 5). *Cont vs Pio (p = 0.004); *Cont Clo vs Los (p = 0.014); *Cont Clo vs Pio+Los (p = 0.001).

improve vasorelaxation to acetyl choline in the aorta of diabetic rats.[10,24] Majithiya and colleagues reported that treatment with pioglitazone reduced blood pressure, reduced oxidative stress and restored endothelial function in STZ-induced diabetic rats. The fact that pioglitazone reduced oxidative stress may have been a cause of the reduction in blood pressure.

The protective effect of pioglitazone against oxidative stress may prevent the breakdown of NO, which may improve vascular function. Similar observations were made by Bagi and co-workers that pioglitazone increased NO bio-availability and reduced oxidative stress in coronary arterioles of mice with type 2 diabetes.[25] Matsumoto and colleagues reported that chronic treatment with pioglitazone restored impaired NO-mediated, endothelium-dependent relaxation in diabetic rat aortae.[26] It has been shown that reduction in blood pressure in the case of STZ-induced diabetic rats was NO mediated.[4] Calnek and co-workers reported that PPAR-gamma agonists increased NO bioavailability in cultured cells.[27]

Pioglitazone was shown to directly induce a relaxation of rat aortae pre-contracted with phenylephrine, which was inhibited by L-NAME.[10] Similarly, indomethacin-treated vessels incubated with pioglitazone markedly reduced the phenylephrine contractions.[3]

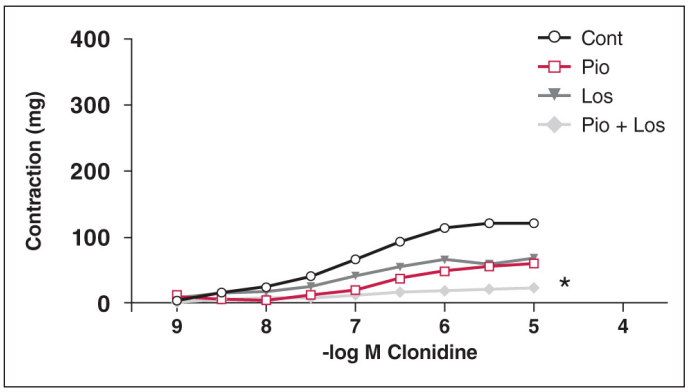

Figure 7. Effects of pioglitazone and losartan on the response of aortic segments to increasing concentrations of clonidine in DM group. Cont: control, Pio: pioglitazone, Los: losartan, Pio+Los: pioglitazone + losartan. Values are expressed as mean ± SEM (n = 16). *Cont vs Pio+Los (p = 0.005).

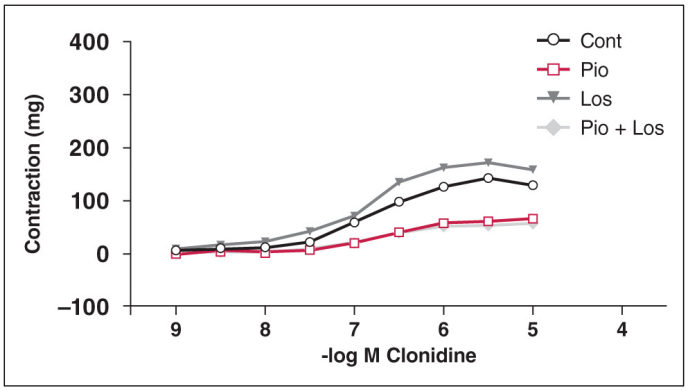

Figure 8. Effects of pioglitazone and losartan on the response of aortic segments to increasing concentrations of clonidine in the HT + DM group. Cont: control, Pio: pioglitazone, Los: losartan, Pio+Los: pioglitazone + losartan. Values are expressed as mean ± SEM (n = 13).

Although most researchers agree that the sensitivity to phenylephrine was unchanged during the early stage of diabetes (up to 12 weeks in STZ-induced diabetic rats), they disagree on the response to phenylephrine. Agrawal and McNeill reported an increase in contractility in response to phenylephrine,[28] Pfaffman and co-workers reported a decrease,[29] and Scarborough and Carrier and White and Carrier reported no change.[30,31] In contrast, studies that extended the diabetic duration up to 43–52 weeks have demonstrated a consistent increase in sensitivity to noradrenaline in rat aortae[32] and mesenteric arteries[33] from STZ-induced diabetic rats.

In our study, we suggest that our diabetic rats did not have enough time to develop a sufficiently severe degree of vascular dysfunction to manifest an effect to phenylephrine. From our results, acute pioglitazone/losartan pre-treatment did not significantly change the maximum contractile responses to phenylephrine in the control, diabetic or hypertensive rats.

We attempted to determine whether these drugs affected the endothelial modulatory responses to vasoconstriction produced by phenylephrine. Sensitivity of the aortic rings to phenylephrine was decreased in the presence of pioglitazone and/or losartan. The glitazones have been shown by Asano *et al*. to decrease smooth muscle cell contractility,[34] and by Dormandy *et al*. to cause improvement in vascular function.[35] We believe, however, that the

blunted adrenergic responses observed in the presence of glitazones were mediated by the action of these drugs on the endothelial cells, since the effect disappeared when the endothelium was removed in a study Mendizabal and co-workers.[21]

Conclusion

In this study, *in vitro* experiments were carried out to investigate the direct effect of pioglitazone and/or losartan on aortic rings of control, diabetic, hypertensive and hypertensive diabetic rats. Our results demonstrate that vascular sensitivity to an alpha adrenoceptor agonist was decreased in the presence of pioglitazone and/or losartan in diabetic and/or hypertensive rat aortic rings. We postulate that these results explain at least in part the beneficial effects of pioglitazone and losartan for hypertension and diabetes. The mechanism of action of pioglitazone and losartan to improve vascular reactivity may be as a result of intracellular protection from oxygen free radicals. Our findings suggest a possible beneficial combination of thiazolidinediones and angiotensin receptor blockers for treatment of diabetes and hypertension.

Further studies are required to elucidate the effects of pioglitazone and losartan on alpha receptors and on the mediators of NO metabolism. It is also remains unclear how pioglitazone and losartan inhibited alpha-2 receptor activities in our rat aortic rings. Further investigation is needed to clarify these underlying mechanisms.

Acknowledgements

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Is the relationship of body mass index to severity of coronary artery disease different from that of waist-to-hip ratio and severity of coronary artery disease? Paradoxical findings

AMIR FARHANG ZAND PARSA, BAHAREH JAHANSHAHI

Abstract

Background: **Although for decades there has been controversy regarding the relationship between obesity and coronary artery disease (CAD), it has been assumed that high body mass index (BMI) is a risk factor for CAD. However, the findings of some recent studies were paradoxical.**

Objectives: **The aim of this study was to find a relationship between high BMI and waist-to-hip ratio (WHR) with severity of CAD.**

Methods: **This study was a cross-sectional, prospective study where 414 patients with suspected coronary artery disease, in whom coronary angiography was performed, were enrolled. The mean ± SD of their ages was 61.2 ± 27.4 years (range 25–84), and 250 (60.4%) were male. Regarding cardiovascular risk factors, 113 (27.3%) patients had a history of diabetes mellitus (DM), 162 (39.1%) had hypercholesterolaemia, 238 (57.4%) had hypertension, 109 (26.3%) were current smokers and 24 (5.8%) had a family history of CAD. The mean ± SD of the patients' BMI was 26.04 ± 4.08 kg/m² (range 16–39) and means ± SD of their WHR ranged from 0.951 ± 0.07 to 0.987 ± 0.05. The mean ± SD of the severity of CAD according to the SYNTAX and Duke scores were 17.7 ± 9.6 (range 0–64) and 3.2 ± 1.7 (range 0–12), respectively.**

Results: **In this study, findings showed a negative correlation between the severity of CAD and BMI, according to both SYNTAX and Duke scores ($p \leq 0.001$ and $p = 0.001$, respectively). However, there was a positive correlation between WHR and severity of CAD, according to the Duke score ($p = 0.03$).**

Conclusion: **BMI had a negative correlation with the severity of CAD, but waist-to-hip ratio had a positive correlation with severity of CAD.**

Keywords: body mass index, waist-to-hip ratio, coronary artery disease, SYNTAX score, Duke score

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Although obesity has been regarded as an independent risk factor for coronary artery disease (CAD) by the American Heart Association (AHA) and investigators of the Framingham Heart study in the 1980s and 1990s,[1-3] this has not been supported by recent clinical trials. Moreover, the positive linear relationships between obesity and CAD, as reported by some studies, were as a result of univariate analysis of their data. However, by using multivariate analysis of these study data, which included other cardiovascular risk factors such as diabetes mellitus (DM), hypertension (HTN) and hyperlipidaemia, this relationship was shown to be dramatically reduced.[4,5]

In the Munster Heart study (PROCAM) and similar studies, the positive relationship between body mass index (BMI) and cardiovascular risk factors, with cardiac mortality, which attributed obesity as an independent risk factor, appeared to be due to the associated cardiovascular risk factors that usually accompany obesity.[6-10] In these studies there was also a strong positive correlation between high BMI and other cardiovascular risk factors.

However, findings of recent studies in this regard were opposite to those of previous studies. According to their findings, not only was obesity not a risk factor for CAD but it also had a protective effect on the progression of CAD, which is known as the 'obesity paradox'.[11,12] On the other hand, abdominal adiposity has always been associated with increased cardiovascular disease and mortality rate, independent of patients' weight.[13,14]

This study was designed to evaluate not only the impact of BMI but also waist-to-hip ratio (WHR) on the severity of CAD, based on angiographic findings.

Methods

This study was a cross sectional, prospective study that was conducted in our hospital from September 2009 to March 2011. A total of 414 patients with suspected CAD were enrolled in the study. Patients' mean age ± SD was 61.2 ± 27.4 years (range 24–84) and 250 (60.4%) patients were male.

Coronary angiography was done on all patients. The severity of CAD was measured using the SYNTAX score (the sum of the points assigned to each individual lesion identified in the coronary arteries with > 50% stenosis in vessels > 1.5 mm diameter). The SYNTAX score, a lesion-based angiographic scoring system, was introduced as a tool to grade the complexity of CAD. It was derived from a combination of the AHA classification for coronary artery segments with various other scores,[15,16] and the Duke jeopardy scores (Fig. 1A). The Duke jeopardy score is a simple, effective scoring system for quantifying the amount of myocardium at risk. The Duke

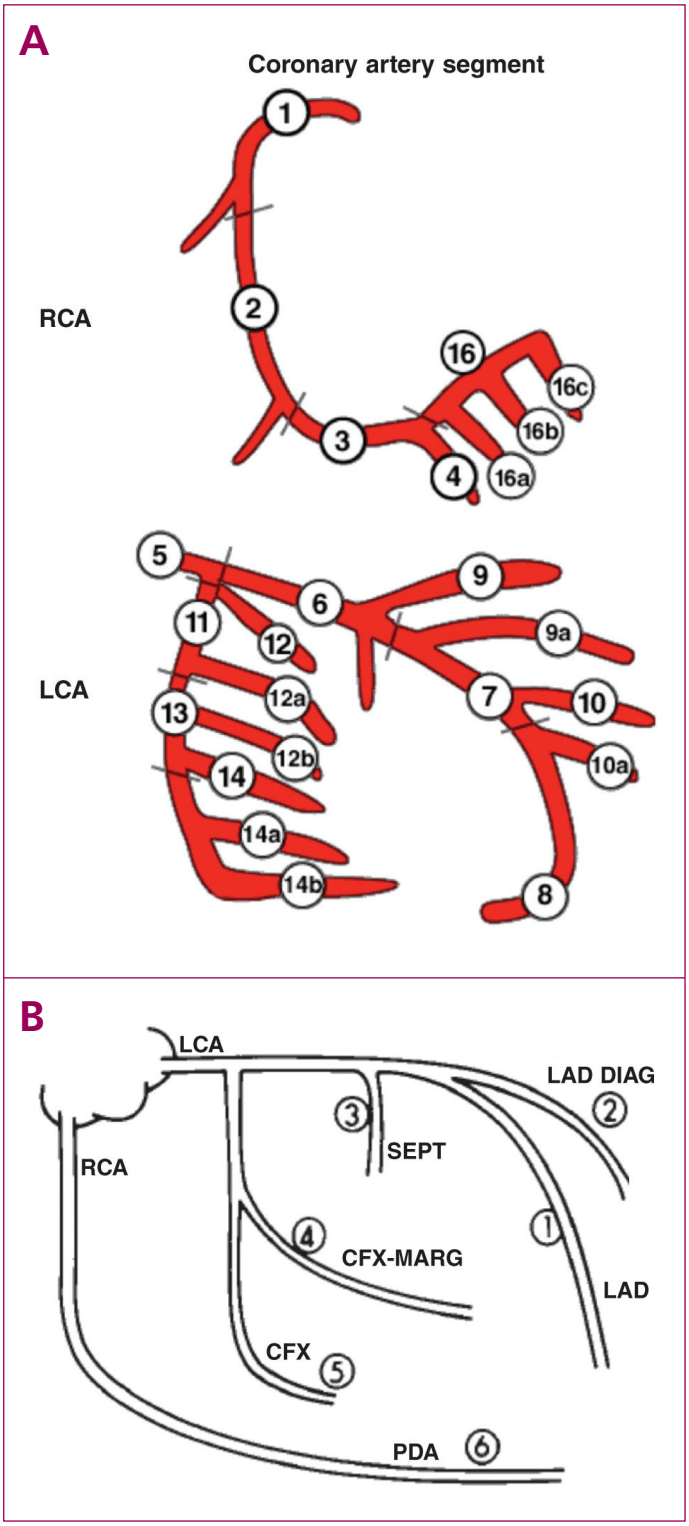

Figure 1. Diagrams of coronary artery tree demonstrating the 16 segments counted in the SYNTAX score (A), and six segments counted in the Duke jeopardy score (B). CFX = left circumflex coronary artery; CFX-MARG = major marginal branch of the left circumflex coronary artery; LAD = left anterior descending artery; LAD DIAG = major diagonal branch of the left anterior descending artery; LCA = left main coronary artery; PDA = posterior descending coronary artery; RCA = right coronary artery; SEPT = major septal perforating artery. (Adapted from Sianos, *et al. Euro Intervent* 2005; **1**: 219–227, and Callif, *et al. J Am Coll Cardiol* 1985; **5**: 1055.)

jeopardy score, developed by Dash *et al*., 1977,[17] and validated by Califf *et al*.,1985,[18] detects the main vessels affected in their large branches, Fig. 1B).

Coronary angiographies of patients were reviewed by two experts who were blinded to the patients' BMI and WHR. Patients were divided into five groups according to their BMI; normal BMI (21–24 kg/m^2), overweight (25–29 kg/m^2), class I obesity (30–34 kg/m^2), class II obesity (35–39 kg/m^2) and class III obesity (> 40 kg/m^2). Also patients were divided into four groups according to their age; 20–39, 40–59, 60–79 and > 80 years old.

Inclusion criteria were patients over 20 years old who had definite indications for coronary angiography, based on their clinical background. The exclusion criteria were patients unwilling to participate in the study.

For the purpose of multivariate analysis, we included in the study evaluations of conventional cardiovascular risk factors, such as HTN (systolic blood pressure ≥ 140 mmHg and/ diastolic blood pressure ≥ 90 mmHg), DM [fasting blood sugar > 126 mg/dl (6.99 mmol/l) and/glycosylated haemoglobin (HbA_{1c}) > 6%], hyperlipidaemia [low-density lipoprotein (LDL) cholesterol > 120 mg/dl (3.11 mmol/l) and triglycerides > 150 mg/dl (1.7 mmol/l)], family history of CAD and cigarette smoking (current smoker: at least five cigarettes/day for ≥ one year).

Statistical analysis

For analysing data, SPSS version 15 (USA, Illinois, Chicago) was used. The Student's *t*-test was used for comparing quantitative variables between two groups and the one-way ANOVA test was used for comparing means of quantitative variables between groups. Logistic regression was used for multivariate analysis of compounding factors. Chi-square and Fisher's exact tests were used for analysis of qualitative variables and a p-value ≥ 0.05 was considered significant.

Results

Of 414 (100%) patients, 250 (60.4%) were male and their ages ranged from 25 to 84 years. The prevalences of DM, HTN, hyperlipidaemia, family history of CAD and cigarette smoking were 27.3, 29.5, 39.1, 5.8 and 26.3%, respectively. Basic clinical and demographic characteristics of the patients are presented in Table 1.

Table 1. Basic clinical and demographic characteristics of patients

Characteristics	Number (%)
Age, mean ± SD (years)	61.2 ± 27.4
Male gender	250 (60.4)
Diabetes mellitu	113 (27.3)
Hypertension	122 (29.5)
Hyperlipidaemia	162 (39.1)
History of CAD	24 (5.8)
Cigarette smoking	109 (26.3)
History of AP	254 (85.5)
History of MI	85 (20.5)

CAD = coronary artery disease, AP = angina pectoris, MI = myocardial infarction.

Table 2. Correlation between BMI and severity of CAD (SYNTAX and Duke scores)

BMI (kg/m²)	Number of patients (%)	SYNTAX score (mean ± SD)	Duke score (mean ± SD)
20–24	169 (40.8)	22.3 ± 17.2	4.01 ± 3.3
25–29	154 (37.2)	16.1 ± 14.6	3.05 ± 2.5
30–34	83 (20.1)	12.1 ± 9.2	2.3 ± 1.1
35–39	8 (1.9)	10.8 ± 7.04	1.8 ± 1.04
p-value	–	0.01	0.001

BMI = body mass index

The severity of CAD was measured by the SYNTAX and Duke jeopardy scores. For the SYNTAX score, the mean ± SD of the patients' scores was 17.7 ± 9.6 (range 0–64) and for the Duke score, it was 3.2 ± 1.7 (range 0–12). There was a negative correlation between the SYNTAX and Duke scores (severity of CAD) and the patients' BMI ($p = 0.01$ and $p = 0.001$, respectively).The correlation between the patients' BMI and the severity of CAD (SYNTAX and Duke scores) is presented in Table 2.

There was an inverse relationship between obesity and the severity of CAD, according to the SYNTAX and Duke criteria, which has been defined as the 'obesity paradox'. In order to rule out the impact of other cardiovascular risk factors, multivariate regression analysis was performed. Regression analysis revealed a β-coefficient of –0.14 for the Duke score and –0.17 for the SYNTAX score. This means that for every unit increase in BMI there would be a 0.14 and 0.17 decrease in the severity of CAD according to the Duke and SYNTAX scores, respectively. After adjusting for confounding factors, there was still a significantly negative correlation between BMI and severity of CAD ($p = 0.028$ and 0.01, respectively). Meanwhile multivariate analysis revealed a positive correlation between severity of CAD and cardiovascular risk factors (Table 3).

On the other hand, our findings regarding the relationship between WHR and severity of CAD, based on the Duke myocardial jeopardy score, showed a positive correlation between the two variables ($p = 0.03$). With increasing WHR, the Duke score also increased. The relationship between severity of CAD (Duke score) and WHR is presented in Table 4.

Table 3. Correlation between cardiovascular risk factors and severity of CAD (Duke and SYNTA X scores)

Risk factors	Duke score (mean ± SD)	*p*-value	SYNTAX score (mean ± SD)	*p*-value
Hypertensives	3.6 ± 1.7	0.04	19.1 ± 13.1	0.03
Normotensives	2.4 ± 1.9		14.9 ± 9.5	
Cigarette smokers	3.8 ± 1.2	0.02	20.8 ± 17.4	0.03
Non-smokers	3.07 ± 1.4		16.6 ± 14.2	
Hyperlipidaemics	3.9 ± 1.5	0.001	31.5 ± 18.05	0.001
Normolipidaemics	2.8 ± 1.2		15.3 ± 11.02	
Diabetics	4.1 ± 3.6	0.002	21.5 ± 18.4	0.008
Non-diabetics	2.9 ± 1.3		16.3 ± 9.2	
FH positive	4.5 ± 3.1	0.07	21.9 ± 14.2	0.4
FH negative	3.1 ± 2.3		17.5 ± 10.4	

FH = family history.

Table 4. Relation between WHR and severity of CAD based on the Duke score

WHR (mean ± SD)	Number of patients	Duke score
0.951 ± 0.07	165	0
0.954 ± 0.06	62	2
0.957 ± 0.07	58	4
0.962 ± 0.05	54	6
0.971 ± 0.05	44	8
0.979 ± 0.02	24	10
0.987 ± 0.05	6	12
p-value	0.03	

WHR = waist-to-hip ratio.

Discussion

In this study, there was a paradoxical relationship between BMI and severity of CAD but not between WHR and severity of CAD. Based on the SYNTAX and Duke scores, β-coefficients between BMI and severity of CAD before multivariate analysis were –0.2 and –0.18, respectively. After multivariate analysis, they were –0.17.and –0.14, respectively. This shows an inverse relationship between BMI and severity of CAD.

Controversy regarding the correlation between obesity and CAD, which surfaced a few decades ago, was the motivation for us to conduct this study. Although it seems logical that obesity or adiposity should be accompanied by more accumulation of fat cells everywhere in the body, including vascular walls (atherosclerotic plaques), it must be clarified that first of all, obesity per se is not adiposopathy, and second, the process of atherosclerosis is not a simple process of fat accumulation.[19,20]

The process of atherosclerosis is inflammation as a result of the response to injury in the milieu of high intravascular LDL cholesterol, especially oxidised LDL. It seems that visceral adipose tissue is metabolically more active and pathological than subcutaneous adipose tissue, and induces immunity processes that contribute to atherosclerotic cardiovascular disease.[21-24] The answer to the question raised from the obesity paradox is that atherosclerotic disease does not result from the accumulation of adipose tissue per se but is as a result of adipose tissue dysfunction, or 'sick fat'.[19,23,24]

Rubinshtein and colleagues (2006), in their study on 928 patients with CAD, showed that obesity had an inverse relationship with the severity of CAD but other risk factors such as DM, hyperlipidaemia and male gender were correlated with the severity of CAD.[11] In another study, published in 2007 by Niraj and colleagues, which was similar to our study, the relationship between severity of CAD and BMI according to the Duke score was also paradoxical.[10] Although there are similarities between our study and theirs regarding the inverse relationship between patients' BMI and the severity of CAD, in our study the relationship between WHR and severity of CAD was evaluated simultaneously. Surprisingly, in our study, WHR was correlated with the severity of CAD based on the Duke score.

Moreover, according to the studies of Morricone, Empana and Zhang, which were published in 1999, 2004 and 2008, respectively, abdominal adiposity and severity of CAD were correlated.[12-14] Although their findings were similar to ours regarding correlation between WHR/abdominal obesity and severity of CAD, they did not compare BMI with WHR regarding their impact on the severity of CAD, as we did. These studies showed that, first, high BMI per se was not a risk factor for CAD, and second, high WHR/abdominal obesity was a risk factor for CAD. That means abdominal fat accumulation is more pathological (adiposopathic) than subcutaneous fat accumulation.[19,24]

Although in our study, regression analysis for confounding factors such as DM, HTN, cigarette smoking and hyperlipidaemia revealed a statistically significant correlation between them and the severity of CAD (p = 0.002, p = 0.001, p = 0.04 and p = 0.02, respectively), after omission of confounding factors, there was still a paradoxical relationship between BMI and severity of CAD. β-coefficients before multivariate analysis were –0.2 and –0.18, and after multivariate analysis they were –0.17 and –0.14, based on the SYNTAX and Duke scores, respectively. This showed an inverse relationship between BMI and severity of CAD.

The limitation of our study was that lower BMI (20–24 kg/m^2) was more prevalent (56.2%) in the older age groups (> 60 years), and higher BMI (30–34 kg/m^2) was more common (57.8%) in the younger age groups (40–59 years). As in the study by Niraj *et al*.,[11] it can be concluded that patents with a higher BMI have been evaluated earlier for CAD. This indicates a need for a larger study with more age-matched groups.

Conclusion

The findings of this study, paradoxically, showed a negative correlation between BMI and the severity of CAD, but a positive correlation between WHR and the severity of CAD.

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Association of homocysteinaemia with hyperglycaemia, dyslipidaemia, hypertension and obesity

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Abstract

Aim: **Hyperhomocysteinaemia and the metabolic syndrome are associated with increased cardiovascular risk. We investigated whether there is a link between the metabolic syndrome or its components and homocysteine levels in a population without cardiovascular disease.**

Methods: **From the population sample of 382 participants (286 females and 96 males) we isolated those reflecting the metabolic syndrome and determined their homocysteine levels. We then evaluated the association of homocysteine with hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia, hypertension and obesity, using a significance level of $p = 0.05$. Enzymatic methods were used for all biochemical parameters.**

Results: **We found the statistical relationship between homocysteine and the metabolic syndrome as follows: hyperglycaemia ($p = 0.175$), hypertriglyceridaemia ($p = 0.442$), hypercholesterolaemia ($p = 0.480$), obesity ($p = 0.080$); and hypertension: systolic pressure ($p = 0.002$) and diastolic pressure ($p = 0.033$).**

Conclusion: **We found no statistically significant association between baseline plasma homocysteine levels and the metabolic syndrome, except for hypertension.**

Keywords: hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia, hypertension, obesity, homocysteine

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia, resulting from defects in insulin secretion, insulin action or both. It is associated with several cardiovascular disorders, including angiopathy and platelet hyperactivity, which are major causes of morbidity and mortality in type 2 diabetes mellitus.[1] Atherosclerosis is substantially more prevalent and progresses rapidly in diabetes mellitus.[2]

There are an estimated 23.6 million people in the USA (7.8% of the population) with diabetes.[1] The vascular complication of diabetes mellitus, at its earliest stage, is manifested as endothelial dysfunction,[3] decreasing the bioavailability of nitric oxide, which protects blood vessels from endogenous injuries.[4] Hyperglycaemia inhibits fibrinolysis by decreasing the activity of plasminogen activator and enhances coagulation by activating procoagulants into thrombosis.[5]

Homocysteine is an amino acid derived from methionine. The latter is an intermediate in the conversion of homocysteine to cysteine. Homocysteine is metabolised via two pathways: remethylation, in which homocysteine is converted into methionine, and transulphuration, in which homocysteine is converted into cysteine. In the former pathway, homocysteine acquires a methyl group, either from the conversion of 5-methyltetrahydrofolate into hydrofolate or from the conversion of betaine into the N' N-dimethylglycine.[6] Vitamins B_{12} and B_6 are important in the conversion of 5-methyltetrahydrofolate into hydrofolate and therefore for the remethylation pathway and the metabolism of homocysteine into methionine.[7]

Epidemiological studies suggest hyperhomocysteinaemia to be an independent risk factor for developing atherothrombotic vascular disease.[8] Mechanisms by which hyperhomocysteinaemia causes vascular disease include promotion of atherosclerosis by damaging the inner lining of arteries and promoting thrombosis through pathological collagen activation of the intrinsic pathway,[9] impairment of thrombolysis, increased production of hydrogen peroxide, endothelial dysfunction, and increased oxidation of low-density lipoproteins.[8]

Some of the complications of arterial thrombosis following hyperhomocysteinaemia include coronary heart disease, myocardial infarction, stroke, peripheral vascular disease, miscarriage, pulmonary embolism, retinal embolism and neural tube defect (spina bifida).[9] The homocysteine level may be increased in hypertensive, overweight and obese subjects.[10]

Homocysteine is thought to help regulate glucose metabolism and insulin absorption.[11] Homocysteine has been suggested to contribute to the atherosclerotic process of diabetes mellitus. High homocysteine levels have been reported in diabetic patients,[2,12] and elevated levels are a strong risk factor in these patients.[1] The elevation occurs particularly in patients with type 2 diabetes, as well as in individuals in prediabetic states who exhibit insulin resistance.[13] The levels of homocysteine in such individuals are also influenced by their insulin concentrations, and therapy with insulin and medications such as metformin and glitazones that can either raise or lower homocysteine levels.[12]

The effect of hyperhomocysteinaemia on diabetes and insulin resistance has been reported with unclear synergism.[12] Homocysteine levels have been reported as either low or elevated compared to non-diabetic subjects, reflecting the potential role of homocysteine in the development of macro- and microvascular disease in diabetic patients.[13,1] Shaikh *et al*. found that 58% of their diabetic participants had elevated homocysteine levels and males were predominant in this group.[1] This finding is consistent with that of Schalinske's study.[14]

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These authors reported a strong association between atherosclerosis, hyperhomocysteinaemia and type 2 diabetes in the Japanese population. They concluded that hyperhomocysteinaemia in diabetes mellitus may contribute to the development of chronic complications. Vayá *et al*. established a borderline statistically significant association ($p = 0.008$) between hyperhomocysteinaemia and hyperglycaemia ($p = 0.054$).[15]

Hypertension is a condition where the artery walls are stiffer and present increased resistance to blood flow. This requires the heart to beat more forcefully and increases the pressure of blood leaving the heart. High blood pressure is often called the silent killer because in the initial stages it presents with no symptoms. It is only after an organ in the body has been irritated or damaged, that the consequences of high blood pressure are realised.[16]

Hypertension places stress on the target organs, including kidneys, eyes and heart, causing them to deteriorate over time. Hypertension contributes to 75% of all strokes and heart attacks.[17] One in three African-Americans has hypertension. One African-American dies every hour from the disease, and more than 30% of African-Americans can count hypertension or its complications as the leading cause of death.[17]

The hypothesis that homocysteine may play a role in the pathogenesis of essential hypertension is based on the fact that homocysteine induces arteriolar constriction, renal dysfunction and increased sodium reabsorption, increasing arterial stiffness.[18] Homocysteine increases oxidative stress, which causes oxidative injury to the vascular endothelium, diminishing vasodilation by nitric oxide, stimulating proliferation of vascular smooth muscle cells and altering the elastic properties of the vascular wall, leading to an increase in hypertension.[18] These authors concluded that homocysteine may contribute to blood pressure elevation. Atif *et al*. observed that plasma homocysteine was raised in most patients with hypertension.[19] The authors found in their study that 80% of their hypertensive subjects were hyperhomocysteinaemic.

Karatela and Sainani found a high prevalence of hyperhomocysteinaemia associated with raised blood pressure, with raised systolic and diastolic pressures.[10] Nabipour *et al*. reported significantly higher homocysteine levels in subjects with high blood pressure.[20] Vayá *et al*. however found no statistically significant association ($p = 0.008$) between hyperhomocysteinaemia and hypertension ($p = 0.229$).[15]

In large community-based studies, plasma homocysteine was found to be cross-sectionally associated with blood pressure, especially systolic pressure, unadjusted for gender and age.[21,22] The authors however found that adjusted for gender and age, the relationship of plasma homocysteine to the incidence of hypertension was statistically non-significant.

Experimental investigations evaluating the association of homocysteine and blood pressure have not yielded consistent results. Diet-induced hyperhomocysteinaemia has been demonstrated to elevate blood pressure in some investigations but to lower it in others.[21] A positive association of total homocysteine with both systolic and diastolic blood pressure was reported in several clinical cross-sectional studies.[21] These authors found no major relationship between baseline plasma homocysteine level and incidence of hypertension.

Lipids are a group of organic compounds that include, among others, cholesterol, triglycerides, phospholipids, lipoprotein and sterols, which are insoluble in water but soluble in non-polar organic solvents.[23] Fats (solid lipids) constitute approximately 34% of the energy used in the human body.[24-26] Of the lipids, triglycerides and cholesterols [very low-density lipoprotein (LDL), LDL and high-density lipoprotein (HDL) cholesterol] are the components that play a major role in atherosclerosis, the forerunner of arteriosclerosis.[27]

All body cells are capable of LDL cholesterol (LDL-C) synthesis. This favours deposition of cholesterol in the cells and blood vessels. LDL-C is therefore atherogenic. HDL transports cholesterol from the cells to the liver for degradation into bile salts (sodium taurocholate and deoxycholate).[23] HDL-C is therefore anti-atherogenic and protective against the development of atherothrombosis.

High triglyceride levels are significant risk factors for cardiovascular disease and are a marker for atherogenic remnant lipoprotein, such as very LDL-C. Even in the presence of tightly controlled LDL-C levels, evidence indicates that high triglyceride levels and low HDL-C levels are independent thrombosis and cardiovascular risk factors.[28] About half of all deaths in developed countries are caused by homocysteinaemia and dyslipidaemia (hypercholesterolaemia and hypertriglyceridaemia).[29]

According to Rima and Wolfgang, there is an association between hyperhomocysteinaemia and dyslipidaemia, and diabetes mellitus is common to hyperhomocysteinaemia and hypercholesterolaemia.[30] Vayá *et al*. found no statistically significant association ($p = 0.008$) between hyperhomocysteinaemia and low HDL-C levels ($p = 0.491$) and hypertriglyceridaemia ($p = 0.490$).15 However, Nabipour *et al*. found subjects with lower HDL-C levels had higher homocysteine levels ($p = 0.001$).[20]

Obesity is characterised by excess body fat due to an imbalance between calorie intake and expenditure. Causes of obesity include high calorie intake, lack of exercise and genetic susceptibility or psychiatric illness.[31] Obesity is defined as a body mass index (BMI) greater than 30 kg/m^2.[32]

Two patterns of obesity are central (visceral) obesity and peripheral obesity. The former is more common in males and carries a higher risk of coronary heart disease, as well as various forms of metabolic derangement, including dyslipidaemia and impaired glucose tolerance. Peripheral obesity is when fat accumulates in the gluteo-femoral area. It is more common in women but less associated with cardiovascular risk, as a complication of arterial thrombosis.[33] Obesity is an independent risk factor for the complications of atherosclerotic vascular disease, such as myocardial infarction and stroke and has been found to elicit and increase the risk of arterial thrombosis.[6,34]

Obesity affects about 1.3 billion people worldwide, and 3.0 to 20.4% of South African males and 25.9 to 54.3% of females.[32,35] Karatela and Sainani observed an increased prevalence of hyperhomocysteinaemia in overweight and obese subjects.[10] Nabipour *et al*. found no significant association between homocysteine level and BMI in a study of the relationship between the metabolic syndrome and homocysteine levels.[20] However, Vayá *et al*. found in four studies that increased homocysteine levels were related mostly to abdominal obesity.[15]

Sanlier and Yabanci found increased body weight to be associated with hyperhomocysteinaemia, but without gender differences.[36] El-Sammak *et al*. also found hyperhomocysteinaemia to increase with age, possibly because of the presence of other factors that raise plasma total homocysteine levels with age, especially increased deterioration in other organ functions.[37]

Methods

The study was cross-sectional and prospective. Participants were recruited by trained field workers and consented voluntarily in

writing. Ethical approval was obtained from the Tshwane University of Technology Ethics Committee (Ref: 2010/09/004). A standard informed consent form was signed by all participants.

A questionnaire was used to obtain information on demographic characteristics, lifestyle, eating habits, health conditions such as surgical operations, diabetes mellitus, previous arterial thrombosis, previous pulmonary embolism, hyperlipidaemia, kidney problems, obesity/overweight and heart failure. Cardiovascular disease was one of the ailments that no participants reported to be suffering from.

Fasting blood samples were collected from participants at the Nobody Clinic in Ga-Mothapo. Subjects who had not fasted for at least nine hours before sample collection and could not withdraw medication for that period were excluded from the study.

Blood was collected by professional nurses. One 4.5-ml blood sample was collected from each participant in a sodium fluoride tube for glucose analysis, in a plain tube for triglycerides and cholesterol estimation, and in an EDTA-anticoagulated tube for homocysteine level assay.

The body weight of the participants wearing light clothing without shoes was measured using a weight scale from Omron. The height was measured without shoes in an upright position using the Seca telescopic height-measuring rod. The BMI was calculated using the formula: BMI = weight in kg/(height in m)^2.

Blood pressure was measured using the Omron MI-5. Blood glucose, triglyceride and cholesterol levels were measured using the ILab 300 Plus Chemistry System from Beckman Coulter. Homocysteine was estimated using the Beckman Coulter Synchron system analyser. Enzymatic methods were used for all biochemical parameters.

The diagnostic criteria used for the parameters were set as follows: hyperhomocysteinaemia = blood homocysteine > 15 µmol/l, hyperglycaemia = blood glucose > 7.0 mmol/l, hypercholesterolaemia = blood cholesterol > 5.7 mmo/l, hypertriglyceridaemia = blood triglyceride > 2.26 mmol/l, obesity = BMI > 30 kg/m^2, systolic blood pressure > 140 mmHg = hypersystolic blood pressure, and diastolic blood pressure > 90 mmHg = hyperdiastolic.

The collected data were analysed with Statistical Package for Social Science (SPSS) version 18. The results were expressed in percentages of *p*-values for association. A *p*-value of 0.05 was regarded as statistically significant.

Results

The study consisted of 382 participants. The mean age of the study participants was 38.45 years. The mean values for the studied parameters were as follows: homocysteine 9.44 µmol/l, glucose 5.42 mmol/l, systolic blood pressure 125.65 mmHg, diastolic blood pressure 81.06 mmHg, cholesterol 4.18 mmol/l, triglycerides 1.22 mmol/l and BMI 26.80 kg/m^2 (Table 1).

The associations of hyperhomocysteinaemia with hyperglycaemia (p = 0.175), hypertriglyceridaemia (p = 0.442) and hypercholesterolaemia (p = 0.480) were statistically insignificant. The association of hyperhomocysteinaemia with obesity was found to be partially significant (p = 0.080). The associations of hyperhomocysteinaemia with hypersystolic (p = 0.002) and hyperdiastolic (p = 0.033) blood pressures were statistically significant.

Of the 45 hyperglycaemic participants, three were also hyperhomocysteinaemic, constituting about 6.7%. Of the 39 hypertriglyceridaemic participants, three were also hyperhomocysteinaemic, constituting about 7.7%. Of the 38 hypercholesterolaemic participants, five were also hyperhomocysteinaemic, constituting about 13.1%. Of the 72 participants with high systolic blood pressure, 11 were also hyperhomocysteinaemic, constituting about 15.3%. Of the 84 participants with high diastolic blood pressure, 16 were also hyperhomocysteinaemic, constituting about 19.0%. Of the 95 obese participants, 10 were also hyperhomocysteinaemic, constituting about 10.5%.

Discussion

We estimated homocysteine levels in 45 hyperglycaemic subjects for evaluation of association and found no statistical significance (p = 0.175) (Table 2). Three hyperglycaemic subjects (6.7%) were hyperhomocysteinaemic (Table 3). Different findings about the relationship have been reported above.

Vayá *et al*., in their study of the relationship between homocysteine and hyperglycaemia, found a partial association.[15] Elias and Eng, and Shaikh *et al*. reported that homocysteine levels can be low or elevated in diabetes mellitus.[1,13] These findings and ours are contrary to the findings of Mishra *et al*.[2] and Akali *et al*.[12] who found high homocysteine levels in diabetic patients. They found high levels of homocysteine to be a strong risk factor in diabetic patients. This was supported by the findings of Shaikh *et al*. and Schalinske.[1,14]

Shaikh *et al*. found more than half of their diabetic participants had elevated homocysteine levels.[1] The discrepancy with our results could have been attributable to the influence on homocysteine of insulin concentrations, therapy with insulin and medication.[12] Control of these confounding factors in our study may have improved the level of association.

Table 1. Characteristics of the participants

Variable	Mean ± SD
Age (years)	38.45 ± 17.283
Homocysteine (µmol/l)	9.44 ± 4.13
Glucose (mmol/l)	5.42 ± 2.555
Systolic blood pressure (mmHg)	125.65 ± 19.164
Diastolic blood pressure (mmHg)	81.06 ± 11.351
Cholesterol (mmol/l)	4.18 ± 1.396
Triglycerides (mmol/l)	1.22 (0.83–1.68)
Body mass index (kg/m^2)	26.80 ± 6.20

Table 2. *P*-values for significance of association

Homocysteinaemia	Metabolic disorder	*p*-value
n = 45	Hyperglycaemia (*n* = 45)	0.175
n = 39	Hypertriglyceridaemia (*n* = 39)	0.442
n = 38	Hypercholesterolaemia (*n* = 38)	0.480
n = 72	Systolic blood pressure (*n* = 72)	0.002
n = 84	Diastolic blood pressure (*n* = 84)	0.033
n = 95	Obesity (*n* = 95)	0.080

95% confidence interval and p = 0.05 level of significance.

Table 3. Prevalence of hyperhomocysteinaemia with hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia, hypertension and obesity

Hyperhomocysteinaemia	Metabolic disorder	Prevalence rate (%)
n = 3	Hyperglycaemia (*n* = 45)	6.7
n = 3	Hypertriglyceridaemia (*n* = 39)	7.7
n = 5	Hypercholesterolaemia (*n* = 38)	13.1
n = 11	Systolic blood pressure (*n* = 72)	15.3
n = 16	Diastolic blood pressure (*n* = 84)	19.0
n = 10	Obesity (*n* = 95)	10.5

Prevalence of hyperhomocysteinaemia = number of hyperhomocysteinaemic subjects per number of subjects in the respective components of the metabolic syndrome.

We determined homocysteine levels in 39 hypertriglyceridaemic and 38 hypercholesterolaemic subjects. No statistically significant association was found between homocysteine and hypertriglyceridaemia (p = 0.442) and hypercholesterolaemia (p = 0.480) (Table 2). Three hypertriglyceridaemic subjects had hyperhomocysteinaemia (7.7%) while five hypercholesterolaemic subjects had hyperhomocysteinaemia (13.1%) (Table 3). The insignificant association was supported by the findings of Vayá *et al*.[15] However, Nabipour *et al*. found significant associations between lower HDL cholesterol and high homocysteine levels.[20]

Homocysteine levels were estimated in 72 subjects with high systolic blood pressure and 84 subjects with high diastolic blood pressure, a total of 156 hypertensive subjects. Homocysteine was statistically significantly associated with both systolic (p = 0.002) and diastolic (p = 0.033) blood pressure (Table 2). Eleven hypersystolic subjects (15.3%) were hyperhomocysteinaemic while 16 hyperdiastolic subjects (19%) were hyperhomocysteinaemic (Table 3). These findings are supported by various researchers, who found hyperhomocysteinaemia to be significantly associated with hypertension.[10,20-22]

The association of homocysteine with hypertension may be due to the fact that homocysteine induces arteriolar constriction, renal dysfunction and increased sodium absorption, with increased arteriolar stiffness.[18] It increases oxidative stress, which causes oxidative injury to the vascular endothelium, diminishing vasodilation by nitric oxide. It also stimulates the proliferation of vascular smooth muscle cells and alters the elastic properties of the vascular wall, leading to an increase in hypertension.[18]

On the basis of our findings, the large body of supporting evidence and the mechanisms of association, homocysteine levels can be used to track blood pressure. Hyperhomocysteinaemia reflects a causal effect rather than being concomitant to elevated blood pressure.

In our present study we evaluated 95 obese subjects for homocysteine association with obesity. We found a borderline association (p = 0.080) (Table 2). Ten obese subjects were hyperhomocysteinaemic (Table 3). The association was partly supported by other researchers, who found increased prevalence of hyperhomocysteinaemia in obese subjects.[10,15,36] Depending on age and the pattern of obesity, homocysteine may be significantly associated with obesity. This viewpoint is supported by the findings of Vayá *et al*.[15] and El-Sammak *et al*.[37]

Conclusion

We found no statistically significant relationship between baseline plasma homocysteine levels and hyperglycaemia, dyslipidaemia and obesity. There was, however, a significant relationship between homocysteine levels and hypertension. According to our cross-sectional study, high baseline plasma homocysteine level is a major risk factor for hypertension and can be used in blood pressure tracking in a large, community-based sample. The study supported the hypothesis that plasma homocysteine is casually related to elevated blood pressure.

Additional prospective investigations are recommended to confirm these findings. A study evaluating the association between plasma homocysteine levels and hyperglycaemia after a few days of treatment withdrawal would probably yield better and more reliable results. Unfortunately, withdrawing treatment from diabetic

subjects may be risky, especially in those with high glucose levels. We plan in future to compare homomocysteine levels between participants with and without the metabolic syndrome.

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Diabetes News

Dealing with the emotions of children with diabetes

Having a child or teenager with diabetes adds a new and different dimension to parenting. To love and care for the child and promote all of his or her potential is one dimension – to take good care of diabetes is quite another. Often these goals seem to contradict each other, yet they need not do so.

This is the view of Rosemary Flynn, a clinical psychologist at the Centre for Diabetes and Endocrinology (CDE). She says that while major advances have taken place in recent years in the management of young people with type 1 diabetes, one cannot step away from the psychological repercussions of a challenging, never-ending condition that needs constant management. 'Advances have helped lessen the burden of everyday living for youngsters and reduce their risk of long-term complications but the condition still has an impact on behaviours, self-esteem, sibling and peer relationships, and family dynamics', she adds.

Flynn says that an understanding of the needs and emotions of children at various stages of development can help us to better identify and understand a child's specific needs and emotions at each age. 'This is particularly true for children between birth and 12 years old. Diabetes management in adolescence needs to be tackled very differently', she says. 'Teenagers have a lot to deal with just being teenagers. When diabetes is added to the process, they need both resilience and resourcefulness to manage successfully. Emotional turmoil at times is inevitable.'

Flynn says it all starts with seeing the child as more than just a physical being. 'There is more to managing diabetes than coping with the physical aspects', she says. It involves the whole of the teen – the physical, emotional, social, spiritual and mental dimensions. How well the body copes with the diabetes is strongly linked to how the child thinks, feels and relates to others. Each of these dimensions will have an impact on how the child behaves. She says although changing emotions are a normal phenomenon for anyone, in children with diabetes, they have the potential to make blood glucose levels unstable. The body reacts to emotional trauma or even emotional excitement by triggering chemical reactions, which make blood glucose levels rise. 'When working with a child with diabetes, it is so important to try to understand the child holistically to achieve and maintain optimum health. Focusing on only the physical aspects of the diabetes will never be sufficient to ensure a well-balanced and healthy child who is at peace with managing his or her diabetes.'

Flynn offers some crucial insights for parents raising a child with diabetes:

- Initiative and self-control: these develop progressively with age and maturity and are often influenced by the parenting style of their parents. Both initiative, being able to make the right decision as needed, and self-control, being able to follow the regimen of managing diabetes, will be needed to enable the child to negotiate his or her diabetes.
- Developing a conscience: so much of the successful management of diabetes depends on a well integrated conscience. Every day of their lives, children with diabetes face the temptation to eat too much, to avoid eating, to eat the wrong foods, to avoid injections or finger pricks, to have extra insulin, to avoid exercise, to over-exercise, to falsify blood glucose results, and so on. For children to take responsibility for their own health and make the right choices depends to a large extent on values such as honesty, success, achievement, self-reliance and being co-operative. Having a well-integrated conscience is the key to developing these values.
- Family balance: parenting that is flexible but firm works well in all families. Power and responsibility is gradually given to the children as they grow and develop. Children react better when they have clear limits, expectations and rules, which adapt as they move into their teenage years. The relationship is always respectful and kind and it is one in which the family can solve problems together. Feelings are valued and the connection between parents and children is of utmost importance. Like sailing a boat, your family must roll with the wind and weather the storms and make continuous adjustments as you try to keep the boat balanced. If you can get this right, you will truly be a flexible family and be blessed with the benefits of that.
- Sibling relationships: while siblings can play a significant role in the process of managing the condition, they can also take a great deal of strain because of the diabetes. Parents should find a balance in the way they handle their children. Somehow, they need to give each of their children quality time. They need to find a way to divide the time they have available between all their children without jeopardising the health of the child/children with diabetes, to make each of the children feel loved and nurtured, and to make sure their own needs as a couple and as individuals are met.
- Managing anxiety: research on children with diabetes has found that if too much anxiety is present, such children cope either by avoiding management altogether to reduce their anxiety, or else by becoming so frenetic in their approach to self-management that their stress levels become intolerable. In either case, control of diabetes is lost. Coping with diabetes is always a family

Support groups for children: Youth with Diabetes – Youthwithdiabetes.com
Facebook support group for parents: Kids powered with insulin.

affair. Parents can play a substantial role in how much anxiety is experienced by the child with diabetes whether it be specific fears related to diabetes or fears that arise in their life context. All fears have an impact on how well the child will cope with having diabetes.

- Anger: another deterrent to good management is anger. Angry children may sabotage their diabetes management. Even those children who have accepted their diabetes and usually manage well, sometimes become angry because of the impact diabetes has on their lifestyle. It is important to acknowledge this anger and work with the child to enable them to reduce their anger. 'Anger gives rise to a chemical response in the body and unfortunately for the child with diabetes, this response means that the child develops high blood sugars', she says.
- Depression: another difficult emotion is depression. Depression takes away any motivation to succeed, so handling depression and suicidal feelings is a necessity for children with diabetes. Three ways to help children become more resistant to depression include building their self-esteem, encouraging physical activity, and finding a support group. Support groups and camps for children with diabetes provide a sense of community, particularly when they can see that other children handle their diabetes well.

'Children with diabetes have to learn to live a lifestyle that promotes their health and enables them to function in the best way possible. This lifestyle includes eating foods that are healthy, doing some exercise and taking medication. However, despite all good intentions, they may still falter. It is so important for parents to provide guidance on how to change, and encouragement to sustain the positive changes they make', Flynn concludes.

Diabetes is the most potentially devastating and fastest-growing health crisis of our time

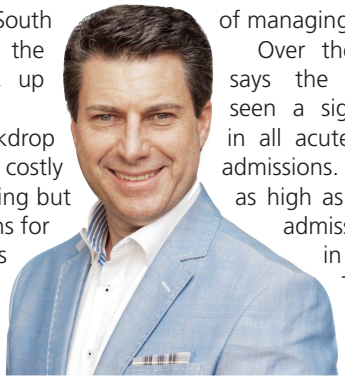
There may be as many as 4.6 million people in South Africa living with diabetes, and possibly the same number at risk of developing type 2 diabetes. Those diagnosed face the risk of life-changing and life-limiting complications unless they receive the care and support they need to manage their condition well.

Grant Newton, CEO of the Centre for Diabetes and Endocrinology (CDE), says it is critical that as a society we start working together to manage the current national crisis posed by diabetes and related chronic health conditions, all of which result in premature and increased cardiovascular risk. 'Not everyone will develop this potentially life-threatening health condition, but diabetes will affect all of us. We are concerned that in South Africa, 68% of people with diabetes remain undiagnosed.'

Newton says that although diabetes is a global problem, it has a local epicentre. In the next 20 years, with 77% of people with diabetes living in medium- and low-economic countries, we expect that the developing world will bear most of the burden of the diabetes pandemic. 'Africa will be particularly hard hit', says Newton, 'with 76% of deaths from diabetes occurring in people under 60.'

In South Africa, four out 10 men and seven out of 10 women are overweight or obese, which is a major risk factor for the development of type 2 diabetes, a largely silent, asymptomatic condition with devastating cardiovascular outcomes. Figures just released by StatsSA report that diabetes became the biggest killer of South African women in 2015, and the second biggest killer overall, up from fifth two years ago.

Newton say against the backdrop of increasingly scarce and costly healthcare resourcing, increasing but preventable costs of admissions for diabetes, and complications of poor diabetes care, it is imperative that the sector urgently starts looking at integrated approaches to preventative, community-based diabetes care.



Grant Newton

'We are clearly lacking critical research funding and resources to improve healthcare and treatment and there is an urgent need for more education and a change in the way diabetes is managed and funded in South Africa'. Newton says while one can't move away from cost restrictions, the real challenge is finding a way of reducing costs without impacting on quality of care. 'We appreciate medical schemes are under enormous pressure to manage their costs, but it is concerning when the focus moves to cost-saving rather than patient service utilisation and improved clinical outcomes. We need to start being far more proactive in treating and promoting patient health, particularly when one considers economic studies from the US showing that in people with diabetes, in-patient hospital care accounts for 43% of the total medical costs of diabetes and that poor long-term clinical outcomes increase the cost burden of managing diabetes by up to 250%.'

Over the last 20 years, Newton says the CDE programmes have seen a significant overall reduction in all acute diabetes-related hospital admissions. 'We have seen a reduction as high as 40% in all-cause hospital admissions and a 20% reduction in the length of hospital stay. This can only be good for funders.'

Newton admits the challenge, however, is that these programmes are not universally accessible to everyone. 'Programmes need to be revised to ensure lower-income patients are not excluded and education platforms need to be extended.' He says that CDE is currently repositioning its offerings to accommodate this need and will be announcing some exciting new changes next month. 'We will also be focusing on how we can partner better with the public sector to extend our postgraduate diabetes training and education.

Currently, CDE through its central office in Houghton, Johannesburg, trains, accredits, administers and audits the biggest network of diabetes providers with specialised postgraduate training in Africa. With 25 endocrinologists, 216 CDE centres of excellence and over 340 contracted general practitioners, the CDE has a unique ability to provide risk-stratified diabetes care and cardiovascular risk management at primary, secondary and tertiary levels of care nationally.

OptiBiotix signs major supply agreement for its microbiome-modulating cholesterol-reduction probiotic

OptiBiotix, a world leader in microbiome modulation, has signed a three-year supply agreement with HLH BioPharma Vertriebs GmbH for its cholesterol-reducing LP_{LDL}® probiotic supplement. Research into the LP_{LDL}® probiotic, presented at Vitafoods Europe in May 2017, demonstrated that it is a safe natural ingredient that reduces blood pressure and cholesterol, key determinates of cardiovascular risk. The probiotic was found to reduce LDL cholesterol by up to 13.9% and blood pressure by 5.1%. This research was carried out by Glenn Gibson, Professor of Food Microbiology, head of Food Microbial Sciences at the University of Reading, UK.

Stephen O'Hara, CEO of OptiBiotix, commented, 'The development of our LP_{LDL}® probiotic product has made cholesterol reduction through microbiome modulation a reality, and we are thrilled to be working with HLH, one of Europe's leading suppliers to the pharmacy market, on this product. The ability to create designer active ingredients that can modify an individual's microbiome to improve health places OptiBiotix at the forefront of global microbiome research and product development, and we anticipate many more opportunities for the LP_{LDL}® probiotic.'

Microbiome modulators in the form of probiotic supplements, such as LP_{LDL}®, may be the way forward for managing long-term conditions such as cardiovascular disease. The reduction of both LDL cholesterol and blood pressure is key to managing the risk of cardiovascular disease. The combination of high blood pressure and cholesterol deposition may lead to chronic inflammation and hardening of the walls of the blood vessels, which greatly increases the probability of suffering a cardiovascular event. Recent research, presented at the 2016 European Society of Cardiology Congress, demonstrated that reducing LDL cholesterol and blood pressure can reduce the lifetime risk of cardiovascular disease by nearly 90%.[1]

The supply agreement grants HLH a non-exclusive license to produce, package and commercialise products containing the LP_{LDL}® strain, and follows HLH's recent order for 100 000 units of LP_{LDL}®. HLH has over 20 years' experience in the distribution of probiotic and natural products under the brand names Lactobact® and Casa Sana® and is one of Europe's leading suppliers of probiotics to the pharmacy market. The company is based in Germany and has established an international reputation for providing high-quality and scientifically validated innovative products. LP_{LDL}® will be supplied as bulk capsules, which will be packaged and branded as part of HLH's market-leading Lactobact® brand.

1. Ference B, *et al.* A naturally randomized trial comparing the effect of long-term exposure to LDL-C, lower SBP, or both on the risk of cardiovascular disease. European Society of Cardiology Congress 2016; August 29, 2016; Rome, Italy. Abstract 3163. http://congress365.escardio.org/Presentation/ESCTV/142571#.WP8ZctLyuUk

New research shows that synthetic prebiotic boosts growth of cholesterol-reducing bacteria in the human microbiome

New research from the Department of Food and Nutritional Sciences, University of Reading, UK and OptiBiotix Health has shown that a naturally synthesised prebiotic can selectively increase the growth of the cholesterol-reducing probiotic, *Lactobacillus plantarum* LP_{LDL}®, as well as enhancing its cholesterol-reducting activity.

This is a ground-breaking development in microbiome modulation, as it is the first time that research has demonstrated the formulation of a truly synergistic synthesised prebiotic that is capable of boosting the health benefit of a particular probiotic. The research was presented by Dr Sofia Kolida at the International Scientific Conference on Probiotics and Prebiotics (IPC) in Budapest on 20 June 2017.

The researchers used reverse-enzyme technology to synthesise a prebiotic, LPGOS, to selectively enhance the growth and cholesterol-reducing activity of the LP_{LDL}® probiotic. LP_{LDL}® was selected from over 4 000 other bacterial strains because of its ability to lower both cholesterol and blood pressure. In a previous study, it was found to reduce low-density lipoprotein (LDL) cholesterol by up to 13.9% and blood pressure by 5.1%. When combined with the LPGOS prebiotic, LP_{LDL}® was found to increase the cholesterol-lowering effect by over three-fold in a 24-hour period.

This discovery indicates that a new kind of healthcare supplement may be possible: a combination of a prebiotic and a probiotic, which are both targeted at the same healthcare benefit. This kind of supplement would be far more effective than existing probiotics at achieving particular health benefits. The researchers suggest that this new healthcare supplement would be called an 'OptiBiotic'.

Dr Sofia Kolida, who presented the research at IPC 2017, commented, 'Using β-galactosidases expressed by LP_{LDL}® (LPGOS) we achieved the synthesis of GOS modulator that works in true synergy with the parent strain, not only increasing its population but also impacting on the biological activity the probiotic was selected for. This is the first time that true synergy has been demonstrated for a synbiotic.'

ECG rhythms CPD

CPD developed by Prof Rob Scott Millar, Cardiac Clinic, UCT/Groote Schuur Hospital

CPD overview: Following the introductory "Approach to Rhythms", this online educational CPD quiz will consist of a series of ECGs with a variety of important cardiac rhythms. Each will be accompanied by a series of questions, followed by a detailed analysis and explanation.

Target audience: Cardiologists, physicians, emergency unit doctors and anaesthetists. Including those studying for FCP and certificate in cardiology.

Total time commitment: ± 30 to 60 minutes.

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CPD certificate: A PDF certificate of completion will be issued on successful completion the CPD.

CPD enrollment fee: Free / no charge.

Important notice: The CPD was made possible by an unrestricted educational sponsorship from Bayer Pharmaceuticals South Africa, which had no control over the content.

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