Diabetes and its impact on wound healing

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Introduction

Diabetes mellitus is a condition which affects the person's ability to control their own blood sugar levels, either because their body doesn't produce enough insulin or because of insulin resistance when cells don't respond to the insulin that is produced (Tortora & Derrickson, 2007). High blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst), weight loss and lethargy. Insulin is the principle hormone that regulates uptake of glucose from the blood into most cells, primarily muscle and fat cells (Dunning, 2009).

Insulin is released into the blood by beta cells (β-cells), found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating (Shier et al, 2010). Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel for cellular metabolism and for conversion into glycogen for storage in the liver. Insulin acts as a key unlocking the cells, so if there is not enough insulin, or it is not working properly, the cells are only partially unlocked (or not at all) and glucose builds up in the blood.

In type 1 diabetes the pancreas cannot produce insulin; symptoms usually begin before the age of 20 and about 15% of people have this form of diabetes (McIntosh, 2006). It is an auto-immune disorder in which the immune system attacks the pancreatic beta cells, ultimately destroying them and halting insulin secretion (Shier et al, 2010). By the time symptoms arise, between 80-90% of the beta cells have been destroyed (Tortora & Derrickson, 2007) see Table 1.

If untreated, type 1 diabetes can result in reduced protein synthesis with protein and fat being used as an energy source; ketone bodies are produced as a result and build up of these ketone bodies leads to metabolic acidosis as dehydration occurs and this lowers the pH of body fluids. Without treatment this state can lead to diabetic ketoacidosis, or diabetic coma, and can result in death (Shier et al, 2010).

Type 2 diabetes develops when the body can still make some insulin, but not enough, or when the insulin that is produced does not work properly (known as insulin resistance). Type 2 diabetes usually appears in people over the age of 40, though in South Asian and black people, who are at greater risk, it often appears from the age of 25. It is also becoming more common in children, adolescents and young people of all ethnicities (Dunning, 2009) possibly as a result of increasing levels of obesity.

Type 2 diabetes accounts for the majority (85%) of all people with diabetes and is treated with a healthy diet and increased physical activity. In addition to this, medication and/or insulin is often required.

Table 1: Types of diabetes

Type 1 Diabetes mellitus	Type 2 Diabetes mellitus
• Affects 15% of the population • It usually affects the younger population (<30 years old) but can present at any age • Genetically predisposed not always • It is an autoimmune condition • Complete lack of insulin production • Symptoms appear rapidly	• Found in 85% of the population • Usually affects older people (>40 years old) but is becoming more common in younger people • Can be genetically predisposed • Lifestyle factors increase the risk • Relative lack of insulin production due to β cell failure and insulin resistance • Symptoms appear gradually

Adapted from McIntosh, 2006.

In 2005 it was estimated that 2.35 million people in England had diabetes; however, only 1.8 million had been diagnosed. Diabetes UK identified that there are 2.6 million people known to have diabetes within the United Kingdom in 2009 (Diabetes UK, 2010).

Diabetes mellitus is a metabolic disorder characterised by hyperglycaemia which predisposes sufferers to chronic complications affecting several organs of the body, including the eye, blood vessels, kidneys and the nerves (Ahmed, 2005). It can have a significant impact on wound healing. In patients who have had a non-traumatic amputation, over 50% have diabetes and in a high number of cases the amputation was preceded by an ulcer or non healing wound (Novak, 2010). Intermittent claudication, absent pedal pulses and ischaemic gangrene are more prevalent in people with diabetes and diabetic foot ulcers affect up to 25% of all diabetics (Dunning, 2009), which should make prevention of wounds and good wound care in diabetic patients a high priority in today's health care system.

Predisposing factors

Identifying and taking action on risk factors recognised in diabetic patients may reduce the number of wounds that develop in diabetic patients and also reduce the time it takes for these wounds to heal. There are many predisposing factors of wounds in the general population and some of the factors can be accentuated in those with diabetes. Reiber and colleagues (1999) found that 63% of diabetic patients presenting with foot ulcers had three common problems: neuropathy, structural foot problems and minor trauma. It has been suggested that peripheral neuropathy was the cause of as many as 90% of foot ulcers (Driver et al, 2007).

It is estimated that of those with diabetes who develop foot ulceration, 34% present each year with a recurrence of a foot ulcer (Dunning, 2009).

The International Consensus on the Diabetic Foot identified several factors associated with the development of diabetic foot ulceration: history of a previous ulcer, neuropathy, trauma, biomechanics, peripheral vascular disease and socio-economic status (International Working Group on the Diabetic Foot, 1999). These factors may also play a part in both the causation and impaired healing of wounds in the patient with diabetes. Understanding the causes of ulceration in the diabetic patient is of great importance to help identify practical solutions which may reduce the incidence and potential loss of limb.

Neuropathy, notably in the lower extremities, is a common problem for those with diabetes. The neuropathy can be sensory, when the patient does not have sensation so loses the protective function of pain and discomfort to alert them to an injury. The sensory neuropathy is thought to contribute to the development of Charcot's foot deformity, progressive destruction of the bones and joints in the foot, which will further raise the pressures at new points on the foot resulting in further ulceration (Falanga, 2005).

Motor neuropathy can place undue pressure on the insensate foot which, linked with a poor vascular supply, can result in the arching of the foot and clawing of the toes, altering the pressure points of the foot and causing callus formation and ultimately ulceration at these new pressure points (Levin, 2002).

Autonomic neuropathy can result in reduced sweating which can give rise to dry skin cause fissures, commonly seen in diabetic patients (Meeking et al, 2006). These cracks provide an entry point for bacterial and fungal infections. Although it is unclear whether having a fungal foot infection poses an increased risk to diabetic patients, it has been implicated as a risk factor for developing lower limb cellulitis (Bristow & Spruce, 2009). Swabs are often taken for bacterial culture and sensitivity in cellulitis, but checking for fungal infections should perhaps be considered.

Both macro vascular and micro vascular disease is more frequent in those with diabetes (Falanga, 2005) and can occur at a younger age and progress faster than in the non-diabetic population (Shaw & Boulton, 2001). Macro vascular disease may be present in the arteries, the main cause of this peripheral arterial disease is atherosclerosis, with fatty deposits accumulating and forming plaques within the arteries, which occludes the lumen over time. Calcification of the peripheral arteries is also common in those with diabetes, commonly affecting the distal tibial vessels (McIntosh, 2006).

Micro-circulatory changes can in part be attributed to the red blood cells being less deformable in people with diabetes who have a higher blood viscosity resulting in the stasis of blood in the small blood vessels (Morain & Colen, 1990).

Also gylcosylated haemoglobin does not readily release it's oxygen to the ischaemic tissues (Stadelmann et al, 1998). It has been suggested that vascular disease is not a common cause of ulceration in itself; however, in conjunction with other risk factors, any minor trauma can lead to ulceration (Boulton, 2006).

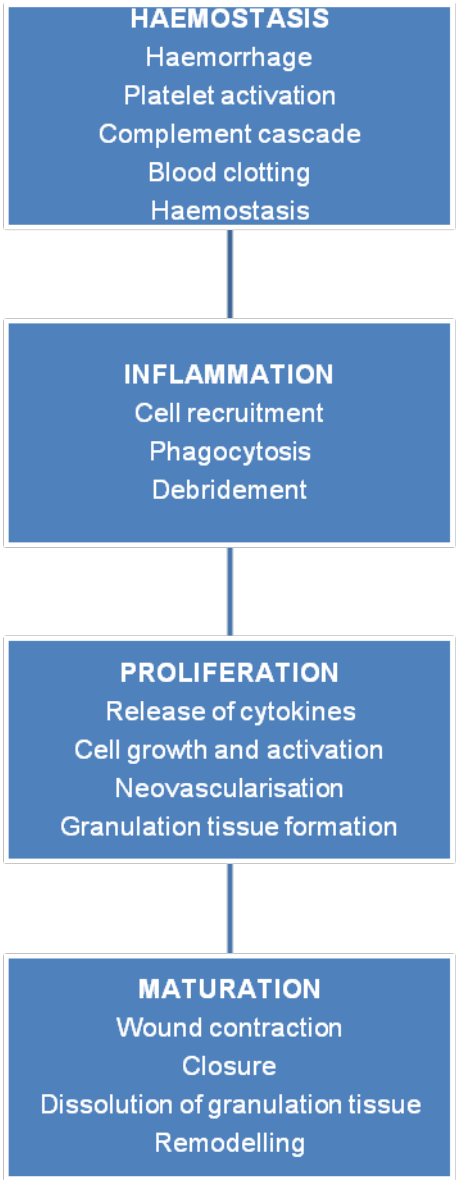
It has also been found that there is a thickening of the basement membrane in diabetic patients (Falanga, 2005) which is linked with poor delivery of oxygen and nutrients to the tissues (see table 2 below).

Table 2 Diabetic risk factors

Problem	Result
Neuropathy – sensory	Reduced /absent sensation signalling damage to the tissues
	Altered gait
- motor	Claw toes
	High arch
	Charcot's osteopathy
	– change in pressure points – callus develops
- autonomic	Reduced sweating causes cracks and fissures
	Potential for infection
Vascular changes	Reduced blood supply via narrow lumen
- arteriosclerosis	Potential for occlusion
- higher blood viscosity	Stasis of blood in small vessels
- glycoslyated haemoglobin	Less oxygen released to tissues
Thickened basement membrane	Reduced diffusion of nutrients and oxygen

Normal wound healing

Under normal circumstances the first stage in wound healing is to achieve haemostasis, reducing blood loss and preventing the entrance of potential pathogens to enter the body (Docherty & Sparks-Defriese, 2007). This stage is quickly followed by an inflammatory phase, when the major cells involved are pro-inflammatory cells, neutrophils initially followed by macrophages which orchestrate the process of cleaning up debris and neutralising pathogens. There then follows a proliferative phase when new tissue is created, new blood vessels and matrix construction to fill the deficit. The maturation phase then increases the tensile strength of the new tissue and reduces the blood supply to the damaged area (Docherty & Sparks-Defriese, 2007) (see box 1).



Box 1: **Normal sequence of events in wound healing**

Compromised wound healing

Wounds in patients with diabetes can and do heal. However, the process may well take longer than healing would take in patients without diabetes, but the healing process is impaired rather than prevented (Falanga, 2004). A non healing wound is prone to complications which can delay the healing process, but in addition to this delay have a significant negative effect on both patient and family. These complications include functional limitations, including alteration in gait and difficulty in walking;
infection including cellulitis, abscess, osteomyelitis; gangrene and septicaemia and possible malignant changes (Menke et al, 2007). Chronic wounds are at risk of developing malignant changes, known as a Marjolin's ulcer, an aggressive form of squamous cell carcinoma (Stadelmann et al, 1998).

Vascular changes in people with diabetes account for some of the problems with wound healing. These changes include a higher prevalence of macro vascular disease and microcirculatory changes which can appear early in diabetes (Falanga, 2005). Reducing the blood supply to the area and directly to the wound bed can have a huge impact on the speed of healing and the patients ability to prevent further complications e.g. infection.

Hypoxia in a wound bed will impact greatly on the healing potential of the wound. In some instances it can be the cause of the wound in the first place, for example in acute arterial occlusion, but even if not a direct cause reduced oxygen can impact detrimentally on the healing of that wound. The thickened basement membrane also reduces the delivery of oxygen to the tissues surrounding the capillary (Falanga, 2005). Hypoxia plays a part in stimulating angiogenesis, the development of new blood vessels and fibroblast proliferation in the early stages of the healing process (Stadelmann et al, 1998). However, if the oxygen tension does not improve then the fibroblasts cannot produce collagen and so healing is impaired (Hunt & Pai, 1972). Hypoxia in the wound bed also plays a role in allowing bacterial invasion of the wound bed.

It is well documented that the inflammatory phase is altered/impaired in the diabetic patient (Lioupis 2005; Kidman 2008). Kidman (2008) postulates that this could, in part, be due to the thickening of the blood vessels, therefore reducing the numbers and speed in which leucocytes reach the site of injury, an idea supported by Marshall (1993). Furthermore there seems to be some evidence to suggest that even if leucocytes are present their phagocytosis ability is significantly impaired (Lioupis, 2005). To compensate for this impaired inflammatory response Kidman (2008), suggests that inflammatory cytokines remain in the diabetic wound much longer than normal, thereby perpetuating and prolonging the inflammatory phase.

The two main cells involved in the inflammatory phase are neutrophils and macrophages. Davis (2008) called neutrophils the “storm troopers” of the immune system and credited them with the largest impact on wounds from an immune response perspective; however it is perhaps the macrophages that have a broader scope when considering the whole on wound healing process. During the early stages of inflammation it is the neutrophils that help debride any debris and necrosis, thereby preventing microbial contamination which could result in infection (Adamson, 2009). Neurtophils die quickly following phagocytosis of microbes. Various proteases and functional proteins (which are carried in their granules) are released, into the wound bed as they work (Davis 2008). Under normal circumstances this is therapeutic as the inflammatory phase is so short lived; however if prolonged the impact on wound healing can be considerable, as over time these can cause tissue oedema and local damage (White, 2003).

As neutrophil numbers fall, it is the macrophages that become active. Macrophages continue to debridement through phagocytosis and also remove the dead neutrophil cells. It has also been suggested that macrophages play a role in stopping neutrophil activity (Dovi & Di Pietro, 2003). Throughout this time they release growth factors into the wound bed, stimulating proliferation of fibroblasts and angiogenesis (Adamson 2009).

Wound infection according to Penhallow (2005) disrupts normal wound healing, however to what extent is still under debate. What is not under debate is that patients with diabetes are predisposed to developing wound infections (Falanga, 2005; Edmonds & Foster, 2006). Marshall (1993) felt this was directly related to the effects of hyperglycaemia; bacteria thrive on the increased glucose available whilst at the same time, hyperglycaemia has been shown to inhibit the action of neutrophils in combating infection (Marshall, 1993). Classic signs of infection are often absent or diminished. This is attributed to neuropathy and ischaemia which impairs the normal inflammatory response (Edmonds & Foster, 2006). Unfortunately impaired neutrophil and macrophage function, coupled with diminished signs and symptoms of infection in diabetic patients, can lead to rapidly spreading infections that can result in limb threatening cellulitis, abscesses and osteomyelitis (Falanga, 2005).

Therefore in the diabetic wound it is perhaps not surprising that necrosis and sloughy tissue is often problematic (McIntosh 2006), with frequent manual debridement necessary in the diabetic foot ulcer. With such a delicate balance between therapeutic and detrimental levels of neutrophils and macrophages appearing to orchestrate to some degree this balance, it is hardly unexpected that diabetic patients suffer from compromised wound healing.

Even in acute surgical wounds diabetic patients still suffer from increase infection rates and associated wound complications (Talbot, 2005; Zerr et al, 1997). Talbot (2005) questioned whether increased surgical site infections (SSI) were due to chronic poor glucose control or acute alterations to serum glucose levels peri-operatively, or even both. Whist Zerr et al reported significantly reduced SSI's in diabetic patient following implementation of a protocol which maintained blood glucose levels at less than 200mg/dL immediately post operatively, equivalent to 11mmol/l. Infection rates were still higher than typical open heart surgery infection rates in non-diabetic patients. Talbot (2005) further proposed that it is not simply glycemic control that increases the risk of SSI's in cardiothoracic patients, obesity is a known SSI risk; With 90% of all newly diagnosed type 2 diabetics being overweight there is clear correlation. Carriage of *Staphyloccus aureus* has also been shown to increase the risk of staphylococcal surgical site infection. Studies have shown diabetic patients have an increased *Staphyloccus aureus* colonisation and therefore increase the likelihood of SSI's (Talbot, 2005).

Irrespective of why diabetics are predisposed to infection it is essential that immediate management strategies are implemented, a view shared by McIntosh (2006). Only by proactively managing wounds in the diabetic patient can we attempt not only to reduce the risk of infection but also complications associated with infection. Pre-operative skin preparation may have a large part to play in reducing post operative infection in these patients.

Proliferation follows the inflammatory phase, and can be compromised in the diabetic patient as the cytokine (or chemical messenger) profile of the wound bed can be altered. Because of the high numbers of inflammatory components, including tumour necrosis factor alpha (TNFα), there is a reduction in the factors which promote proliferation: for example: platelet derived growth factor (PDGF), with pro-inflammatory cytokines dominating the proliferative cytokines. There is also a suggestion that fibroblasts are less responsive to growth factors (Loots, 2002). This results in slower production of the matrix in the wound bed as the proliferative activity is suppressed (Lobmann et al, 2002). Essentially the inflammatory processes are poorly regulated and promote continued inflammation, rather than moving forward to the proliferative phase of healing in a diabetic patient's wound (see table 3). The quality of the extra cellular matrix laid down can be poorer than in non diabetic patients, with reduced levels of transforming growth factor β (TGFβ) found, resulting in less tensile strength and less collagen deposition (Bitar & Labbad, 1996).

Table 3 **Impaired wound healing in the diabetic patient**

Normal wound healing	Impairment in diabetes
Haemostasis	Poor vascular supply Increased risk of infection entering
Inflammation	Slow recruitment of neutrophils Neutrophils remain after 72 hours Persistent inflammation
Infection	Hyperglycaemia allows bacterial growth Slow/ineffective neutrophil & macrophage activity
Proliferation	Reduced tensile strength Reduced collagen deposition Reduced fibroblast activity
Maturation	Reduced tensile strength

Summary
Wound healing is usually a well organised complex series of events which can be impaired in the presence of a chronic illness such as diabetes. It takes an understanding of the wound healing process and the effects of diabetes to promote the healing of these complex patients with what can be potentially life threatening wounds.
Chronic wounds cost a huge amount of money to treat, with important effects being the number of lost work days, decreased productivity and disability payments plus the additional cost of rehabilitation. The total sum is incalculable. Irrespective of this financial cost, the psychosocial issues affecting patients and their families are immense.
As a result, good practice in identifying potential barriers to healing can have a significant impact on the patient. When looking at the quality of life issues in diabetic foot ulcer care, it would appear that patients are less concerned with how the ulcer is treated; the quality of life and patient satisfaction increases when the ulcer heals, suggesting the outcome may justify the means in diabetic foot ulcer care (Armstrong et al, 2008).

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