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Nutritional Treatment of Diabetic Foot Ulcers - A Key to Success

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1. Introduction

Diabetic Foot Ulcers (DFUs) represent a frequent occurrence in the diabetic population and up to 15% of these subjects may be expected to develop a foot ulcer at least one time in his/her life[1,2]. DFUs cause personal, social and economic problems and are a serious risk factor for death[3,4]. These ulcers can be broadly classified as neuropathic, vascular[5] or mixed, although the pathogenesis is much more complex. Biochemical[6], hygienic[7], structural deformity[8,9], dynamic, pressure, skeletal, nutritional, socioeconomic factors, reduced antibacterial activity[10,11,12], workplace influences, all concur to cause and maintain the lesion. A multicenter study attributed 63 percent of diabetic foot ulcers to the critical triad of peripheral sensory neuropathy, trauma, and deformity[13]. Most often healing requires the cooperation of many specialists, including surgeons, podiatrists, wound nurses and endocrinologists. In many cases, the definitive treatment demands minor or major surgery.

While the treatment of vascular ulcers is straightforward and requires a bypass or a radiologic procedure if the damage to the limb is to be limited or cured, the treatment of neuropathic ulcers is much more complex. Most often relief of the abnormal pressure does not lead to the healing of the ulcer, rather these wounds are characteristically chronic, with alternating periods of partial improvement and relapse. Sometimes a superimposing infection worsens the clinical condition. These ulcers in general do not lead to major amputation of the limb but frequently cause considerable economic, social and psychological burden on the patient and his relatives.

2. Etiology of the ulcer

The distinctive characteristic of the diabetic ulcer is the tendency to become chronic. There are many definitions of "chronic". The American Heritage Medical Dictionary and Stedman's Medical Dictionary define chronic ulcers as a "longstanding ulcer with fibrous scar at its base. A thorough search through the literature does not give an exact definition of this term. Sometimes one can read of "ulcers lasting more than six months" but this ignores the wide array of biological backgrounds and the phenotypic presentations of these ulcers. We propose an equally subjective but more realistic definition: "*an ulcer lasting more than one*

could expect on the basis of previous experience in nondiabetic subjects". The characteristic chronicity of the DFU was one of the bases for the diagnosis of diabetes before the introduction of the blood glucose assay. This idea penetrated the lore, and it is still possible to hear sentences like "I do not have diabetes, my ulcers heal quickly".

Chronic neuropathic ulcers usually occur as a result of a repeated trauma in the most exposed areas of the foot and ankle. However, not infrequently, may be the result of an acute trauma that is not recognized at the time of injury due to the relative pain insensitivity. The acute pathologic process is probably different and the outcome more favorable in the acute events versus the chronic ones.

The neuropathic ulcers have many concurrent factors that come into play to initiate and sustain the ulcer process. Among the risk factors, the presence of peripheral neuropathy with the consequent reduced or absent pain sensation, of bone deformity that exposes the bone heads to an abnormal load, and of trauma are prevalent[13]. Some form of diabetic neuropathy is present in nearly 65 % of diabetic patients. Fifty percent of these have a peripheral[14] that causes the loss of protective sensation. The often associated autonomic nerve dysfunction decreases sweating and causes thin, dry, fissured skin[15,16] that breaks easily. This autonomic dysfunction is one of the main causes of the severely damaged "Charcot foot"[17,18]. Trauma of any kind almost always has an initiating role. Acute wounds often are inadvertently self-inflicted during nail care or minor inadvertent injuries. Due to concomitant nerve damage, patients may not recognize or remember the trauma. The use of heaters to warm the feet or of overheated water to wash may cause burns or blisters that later develop into chronic wounds. The initiating factor in chronic pressure wounds most often is the repeated impact of an ill-fitting shoe on one area of the foot. Furthermore, diabetic patients have a peculiar rigidity of the joints that do not allow the foot to mold to the shoe or the floor[19], thus creating an abnormal pressure and increasing the risk of injury. In many instances, calluses are an independent cause of injury, and is not uncommon to discover an ulcer beneath a callus.

Diabetic neuropathies appear with such wide array of different clinical presentations and in so many different places, sometimes symmetrically, less frequently as mononeuropathies, that finding a common cause has till now been impossible.[20,21] The most obvious culprit is hyperglycemia[22], and at least at the beginning of the disease the normalization of the blood glucose can frequently revert to normal symptoms and signs of neuropathy.[23,24] Chronic hyperglycemia plays an important role in the appearance of neuropathy. It is well known from the Diabetes Control and Complication Trial (DCCT) that strict control of blood glucose in newly diagnosed non complicated type 1 diabetics decreases the development of peripheral neuropathy in 60% of the cases over 5 years [25,26]. However, the exclusive role of hyperglycemia has been challenged on the basis of the failure in some cases to achieve improvement of neuropathy with blood glucose control[27,28] and other observations among which the increased incidence of this condition in prediabetes, [29,30,31] a state in which the blood glucose is still normal. Alternatively, a role of insulinopenia has been suggested.[32,33] Insulin receptors are present in the peripheral nervous system, and it is conceivable that any malfunction of insulin delivery[34] may damage the function of neurons. There is also proof that in an experimental model of diabetes, a modest reduction of insulin levels even without an increase of the blood glucose levels can reduce the pain threshold.[35,36] Thus it is possible that the insulin level required to regulate the nerve function is higher than that needed for

glucose control. Further, neuropathy can appear early also in type 2 diabetes[37,38] where at least in the prediabetic stages, there is a compensatory hyperinsulinemia coupled with an increase in insulin resistance. This and the previous observation that a higher level of insulinemia is probably required for the regulation of the nervous than the glycemic system may point to a role of insulin resistance. In this case, the compensatory hyperinsulinemia could be present for many years and be effective to prevent the occurrence of overt diabetes, but not to prevent the nerve damage. Or, in turn, the insulin resistance could involve the nervous receptors to a higher degree than those involved in glucoregulation. It has also been shown that Insulin Growth Factor 1 (IGF1), a molecule that mimics many insulin effects,[39,40,41] induces recovery of the nerve function in rats[42]. Taken together, these hypotheses fail to explain the pathogenesis of diabetic peripheral neuropathy and do not confirm an exclusive role of hyperglycemia. On the other hand, there is no doubt that hyperglycemia causes the microvascular damage frequently associated with the DFU. In a recent study the Authors found a graded association between HbA1C and carotid Intima Media Thickness (IMT) that is currently considered the best marker of progression of atherosclerosis.[43] In this study LDL and HDL cholesterol, plasma triglycerides, and waist-to-hip ratio were significantly associated with HbA1c after multivariable adjustment. Among other factors interfering with healing at the cellular level, the prevalence of infections in diabetics should not be overlooked. Chemotaxis, phagocytosis and all the bactericidal actions of neutrophils are impaired in uncontrolled diabetes[4445]. Also the formation of Advanced Glycation Endo Products (AGE), that can bind to specific receptors on the leucocyte membrane (RAGE), may further impair the leucocyte antibacterial activity.[46] Thus, at present we have not identified a distinctive cause nor we have a definite role for the co-causal factors. One hypothesis put forward to explain the appearance and/or the progression of diabetic neuropathy is that impairment of synthesis of proteins may be the primary insult leading to the centripetal necrosis of the neuron [4748,49,50,51]. Because this aspect is strictly connected with the topic of nutrition we will deal with it later in this chapter. This and many other hypotheses and their support were recently discussed in depth[52] and are beyond the scope of his chapter

3. The body composition of the subjects with an ulcer

The body of a diabetic is different from the body of a person who has a normal blood glucose level. The well known changes at the molecular level, notably the accumulation of AGEs[53] cause in time morphological changes of the tissues, with diffuse damage to the vascular walls, reduction of the body cell mass and lean body mass[54], skin stiffness and prevalence of fat.

What we broadly define lean body mass is in reality a composite of what is mostly the structural - protein component of the body including muscle, parenchymal organs, red blood cells, enzymes, mitochondria and the like,[55] and has a critical role in maintaining the integrity of the body and permitting the survival. Although surprising there are very few studies of the body composition of type 2 diabetic subjects. To fill this gap we compared the body composition of 244 subjects with type 2 diabetes mellitus and demonstrated a reduction in the Body Cell Mass index (an index of the % mass of cells normalized for the actual height of the subject) in both sexes versus 266 non diabetic matched controls. Furthermore in 715 diabetics we also demonstrated that this reduction was proportional to

both the prevailing level of HbA1c in the last year and the duration of disease, although with the multiple regression analysis the former appears to account for most of the actual reduction[52].

There are many possible explanations for the protein/lean body mass loss: (1) the body of the diabetic is in a continuous catabolic state due to insulin deficiency and to the phenomenon of neoglucogenesis continuously turning aminoacids and fat into harmful glucose. This process lasts throughout the day in uncompensated diabetes[56] without interruption at mealtime and is proportional to the blood glucose level[57], in accordance with our observations. (2) Most diabetics have a persistent microalbuminuria, which represents another source of protein loss[58] (3) the wound itself is a source of protein loss proportional to the size and depth of the lesion.[59] (4) Because of the concomitant kidney damage these patients are frequently put on a protein reduced diet, on unsupported grounds[60], thus aggravating their protein depletion.

Furthermore the presence of the wound tends to change the metabolic environment towards catabolism: the secretion of proinflammatory cytokines in proportion to the size and the condition of the lesion increases the insulin resistance deranging glucose metabolism, and drives the body into a catabolic state. This phenomenon is particularly dangerous in diabetics who already have high circulating levels of cytokines secreted by the excess abdominal fat. The increased cortisol secretion as part of the stress response to the wound adds to the catabolism: less energy is derived from the fat mass, and the protein catabolism is increased. In turn the release of aminoacids drives the neoglucogenesis in the liver.

To add further to this catabolic state, diabetic subjects have reduced levels of most anabolic hormones. Beyond the obvious absence or ineffectiveness of insulin on protein metabolism[61,62,63] these subjects have a subnormal level of testosterone (low testosterone syndrome)[64,65,66,67] with a characteristic hypogonadotropic hypogonadism[64] responsible for the decreases the lean body mass. In view of all these events occurring together it is not surprising that most of these subjects are in a protein depleted state. As suggested before, it is possible that the failure of proteins synthesis involved in nerve functioning may result in impaired nerve regeneration and death.[68,69,70,71]

Loss	Catabolism	Reduced supply
Kidney (microalbuminuria) Liver (neoglucogenesis) Ulcer (exudate)	Low testosterone Low GH Fat derived cytokines	Diet Protein losing enteropathy diarrhea

Table 1. Common causes of protein malnutrition in the diabetic

It is thus clear that decompensated diabetes is a catabolic condition further aggravated by the stress reaction and this creates a conflict with the ancestral mechanisms of survival of the body. A better comprehension of the wound healing process can be acquired through an analysis of these processes. The human body is programmed for survival and has a hierarchy of priorities for this aim[72]. The primary need is the conservation of the lean body mass defined as above as a composite of muscle, circulating enzymes, red blood cells, all the parenchymal organs, the immune organ and the water representing the metabolic and structural machinery of the body. Stated more simply the lean body mass is

all that is not fat. Any reduction of this mass poses a risk to survival. This compartment is continuously refilled with the proteins derived from the diet. The average energy need of a healthy young 70 kg person is 2500 cal / die obtained from the diet. Usually 20% of these (125 gr) derive from protein. However in times of abundance, when the lean body mass is replete, the organism deals with the wound as a nutritional priority and any aminoacid and protein supply acquired through the diet are diverted to the wound to promote the closure[73]. This diversion to the skin is a damage to the lean body mass because subtracts the aminoacids from the diet in proportion to the size and the depth of the ulcer. If the lesion is exceedingly large and deep also the protein content of the lean body mass is catabolized to aminoacids to support the repair of the skin. When more than 15-20% [74,75,76] of the lean body mass is lost the survival mechanism changes radically its perspective and the true priority becomes the maintenance of this structure. Under these conditions the body uses all the hormonal and metabolic tools available to support the lean body mass, that includes antibodies and immune cells and almost nothing is left for the wound. The integrity of this lean mass is so critical that its reduction to ≤60% of the initial value usually leads to failure of the immune function and death due to pneumonitis[77].

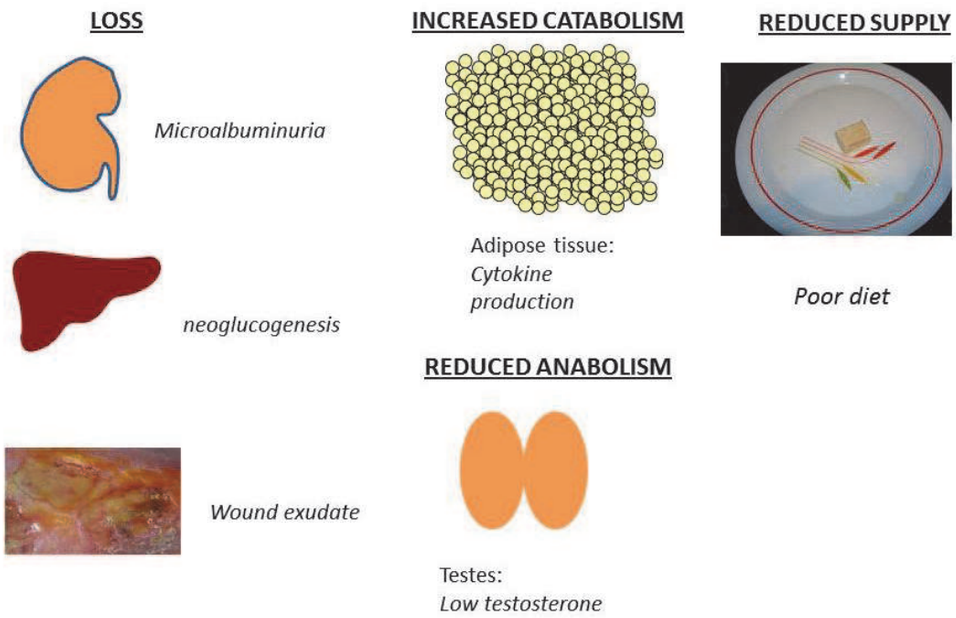


Fig. 1. Main causes of protein malnutrition in diabetes

We should envisage the body as a sophisticated system with a central compartment (Lean Body Mass, LBM) supplying the periphery on demand. If a peripheral lesion (the ulcer) supervenes the central compartment supplies protein until a danger level of depletion is reached. The human body does not have a reservoir of spare proteins, and these have a low energetic yield. Thus a critical level of depletion is reached soon. This phenomenon is even more prominent in the protein depleted diabetics. In these subjects the central compartment of LBM is frequently already in borderline-low conditions and subtracts all the alimentary supply of proteins. In these conditions an ulcer will never heal.

In summary, in the presence of a chronic ulcer in a longstanding diabetic subject, we must always assume the existence of a certain degree of lean body mass (LBM) loss. The Body Bioimpedance analysis (BIA) is a widely used method for estimating the body composition and the presence of this condition. The technology is relatively simple, quick and noninvasive and evaluates the electrical impedance of body tissues, which provides an estimate of total body water (TBW). This value can be used to calculate the fat-free mass (FFM) and body fat (adiposity).In addition this technology can be used to evaluate the body cell mass (BCM). When the BCM is corrected for the actual height of the subject (Body Cell Mass Index, BCMI) gives a very accurate estimate of the total cellular mass and is a useful tool to assess the nutritional state, more so if a previous report is available for comparison to estimate the degree of damage. [78]

Diabetic foot ulcers tend to occur in the advanced stages of the disease. The usual saying that a characteristic of early diabetes is the slow healing of wounds dates back to a period when the diagnosis of the disease was delayed. Today a diagnostic delay only occurs in the poor and the underprivileged. In these subjects the catabolic state is usually well advanced and the skin is thin with widespread loss of the subcutaneous tissue, and a chronic nonhealing ulcer can be a presenting sign of diabetes. We demonstrated in 700 diabetics that at this stage the loss of the lean body mass is already advanced, and that the use of re-feeding solutions containing an increased percentage of proteins can help to recreate the lean body mass[52] and the subcutaneous tissue[79]

Clinical scenario	Favorable	Intermediate	Worst
Wound: Size Caloric / protein requirement	 -Small -low	 -medium -intermediate	 -large -high
Lean body mass	-healthy	Healthy/ slightly reduced	-markedly reduced
Nutrition	Sufficient	Sufficient/scant	Scant
Pathophysiology	External supply redirected in percentage towards the ulcer	External supply partitioned between the ulcer and the fat free mass	External supply redirected towards the lean body mass
Ulcer	Heals rapidly	Ulcer healing delayed /absent	No ulcer healing

Current treatments

Since a single cause of the nonhealing diabetic foot ulcer has not been identified a variety of different products acting on, mimicking, or purportedly having magic qualities, have been introduced on the market without substantial proof of benefit, and often lacking rationale.

Although frequently emphasized, the general condition of the patient, the strict control of his blood glucose and the general nutritional status are too frequently overlooked, mostly

in the general medical or surgical wards, where the attention is focused on the ulcer itself. The concern for the local factors and the commercial pressure of the pharmaceutical companies generated an incredible number of local treatments, including ointments, growth factors and the so called "advanced medications" containing a variety of metals and ions that should stimulate the reparative process. However the use of these substances did not demonstrate any substantial improvement in clinical studies. Although we do not think that these medications have a great role, we must acknowledge that proving the efficacy of these substances in healing ulcers with randomized controlled studies is a complicated and expensive task. It is evident that recruiting an adequate number of subjects with the same duration of disease, a similar degree of diabetic control, and an ulcer of the same characteristics for a randomized controlled trial is very difficult, and unless a substance has truly magical properties the statistical results will be open to discussion[80],[81],[82]

What starts the cascade of problems in the diabetic is an alteration of glucose metabolism that in turn causes a series of metabolic derangements, and the dire consequences that follow. In a recent study the Authors found a significant prevalence of HbA1c $\geq$7% (53 mmol/mol) and HDL $\leq$ 50 mg/dl in diabetic subjects with lower extremity disease versus those without.[83] But if things are so simple, why is the normalization of blood glucose alone not able to induce tissue regrowth and ulcer healing? The answer is that a diabetic foot ulcer only appears after a long period of decompensated diabetes, when the nerves, the skin and all the supporting tissues and structures are already severely damaged or impaired and the simple correction of the causal abnormality is not enough. In this respect is worthwhile to mention the results of the Accord study casting doubt on the feasibility of intensive blood glucose control in diabetic patients with complications. In this study after an average of 3.5 years, 257 people in the intensive blood glucose lowering strategy group died, compared to 203 participants in the standard strategy group. This difference of 54 deaths resulted in a 22 percent increased death rate in the intensive group. Since the presence of a DFU is a complication these results have an important bearing on the treatment of these subjects.[84]

Under normal circumstances the healing of an ulcer requires energy supplied by lipids and glucose. The role of glucose is probably the most complex because this molecule is part of the structural glycoproteins, of some enzymes[85,86] and fuels the inflammatory cells[87]. Lipids for the energetic needs of healing can be obtained from the diet or from fat deposits. As happens for glucose, lipids have multiple functions: the most well known is energy storage, but these molecules also have signaling capacity and are structural components of the cell membrane. Both glucose and lipids must be available for the normal healing processes of the ulcers, but diabetics have a characteristic difficulty disposing of glucose inside the cells that can be only partially reversed with the available treatments. Proteins are structural components of the skin, but these subjects almost always have a degree of preexistent protein deficiency that must be taken into account when planning a diet. Estimating the degree of deficiency is the difficult part because the body composition is an individual characteristic and no "normal values" exist. The available tools to evaluate the degree of LBM and indirectly the degree of protein loss, like Bioimpedance Analysis and Skin Fold Thickness, are only useful in the presence of

previous records of the same subject. The body weight loss, another simple and sequentially available measurement does not give any information on the body compartments and is thus of limited utility. However the presence of a nonhealing ulcer implies the loss of at least 20% of the LBM. When estimating the calorie-protein need of a diabetic the most reasonable option is to err on the excessive side.

Although the role of nutrition is crucial and usually acknowledged, it is surprising how often is overlooked in practice. The most recent edition of the ADA book on the treatment of DFU[88] does not even mention the general condition and the nutritional status of the patient among the aspects to evaluate.

Our hypothesis is that the damage to the tissues is both preventable and at least partially reversible if the treatment is directed towards all the main causal factors. In other words, in our opinion if the vascular blood supply is normalized, the blood glucose level is kept under control, the abnormal pressure is reduced with adequate biophysical support and the texture of the skin is reconstituted there is absolutely no place for growth factors, colloids, metals or whatever else. The diabetic now has the same ability to heal as nondiabetics. The reconstitution of the skin requires the supply of proteins and other biological material that is usually reduced in the diabetic and must be supplied with adequate nutrition. The avoidance of relapses requires attention to postural and neurologic factors.

4. Treatment

The role of the nutritional condition of the patient with a DFU is crucial to the pathogenesis and treatment of the lesion, but infrequently recognized or treated. Accordingly, we think that the term "treatment of the DFU" is a misnomer and should be substituted with "treatment of the subject with a DFU". We suggest a series of steps[89]:

1. Whenever possible the nutritional condition should be assessed as accurately as possible, with Bio-Impedance Analysis, Skin Fold Thickness, Body Weight and Blood chemistry studies (protein electrophoresis, BUN, Hemogram). If previous values are available the change should be included as part of this assessment.
2. The resting caloric requirement should be calculated as 20-25 kcal/kg body weight. This value decreases in the elderly. The value so obtained should be multiplied by 1.2-1.5 according to the severity of the lesion.[90] This figure should be increased if there is evidence of malnutrition.
3. Add the caloric expenditure of activity. All these measurements can be obtained with the use of indirect calorimetry or with the recently introduced non-invasive tools worn at the arm that are worn over a longer period of time. The statistical elaboration of the Bio-Impedance Analysis can yield a reliable estimate of the Basal Metabolic Rate
4. The value so obtained should be multiplied by a "stress factor" that varies from 1.2 for clean wounds, to 1.5 in the case of infected wounds

All these calories should be replaced with an adequate diet, with no less that 20-22% protein given in at least three divided doses throughout the day. These values should be increased by 30-50% according to the co-morbidities of the subject. Paddon Jones suggests that non diabetic elders should have a minimum of 15 g of essential amino acids, equivalent to about

30 g of high-quality dietary protein at each meal.[91]Although there are no fast and hard rules this figure must be increased in the diabetic with a chronic wound.

Another critical component is hydration[92]. We suggest to drink at least 2-3 lt of water per day. In addition to the maintenance of the circulation and the tissue exchange of metabolites, the water induced diuresis helps the body to get rid of the excess glucose.

Some trace substances and vitamins are also absolutely needed for the healing process. In particular Vitamin C, E, Selenium and β-carotene with strong antioxidant properties that antagonize the harmful oxygen free radicals (ROS) present in excess in the chronic wound[93]. Vitamin C is also needed for collagen formation.[94]

The progression of the ulcer should be evaluated with inspection, with photographic records including a ruler close to the lesion, with the biochemical analytes useful to monitor the inflammation and the nutritional state (ESR, Hemogram, CRP, Albumin and Prealbumin levels), and the BIA.

5. The role of supplements

The body of the diabetic is in a general catabolic state and restituting the normal catabolism is a distinctive advantage for the treatment. According to this principle testosterone treatment has been instituted.[95] We use transdermal testosterone supplement in testosterone deficient subjects with apparent reduction in healing time, although we did not conduct a systematic study. Other anabolic hormones have been used with variable results.[96] We have a good experience with an oral nutritional supplement, a blend containing Argine, glutamine and β-hydroxy- β -methyl-butyrate (HMB). HMB is normally present in the muscle, is an active leucine metabolite and a potent stimulator of mTOR (Mammalian Target of Rapamycin), an intracellular protein controlling protein synthesis.[97],[98] Due to this anabolic property, the substance is widely used by the athletes worldwide, and to reverse the effects of aging.[99] Glutamine also has a spectrum of positive effects[100], notably stimulation of protein synthesis and support of immune function.[101],[102] and a positive effect on intestinal integrity.[103] Its effectiveness in collagen formation has also been consistently proven.[104] Arginine also has a positive effect on wound healing[105], and stimulates immune function.[106],[107] Arginine also has a vasodilator action[108] that was exploited for male erectile dysfunction before the introduction of the phosphodiesterase inhibitors. In our experience the use of this blend reduced to 1/3 the time to healing in a group of 12 diabetic patients while improving the lean body mass.[109] We also found an unexpected reduction of microalbuminuria in 16 diabetic subjects under treatment with this blend, which might concur to explain the increase in lean body cell mass[110]

It should be emphasized that the use of anabolic substances or blends is no substitute for an adequate nutrition with enough protein, calories, minerals, vitamins and iron that can be found in the normal Western diet. Therefore, the best nutritional approach to the diabetic patient is: (1) the evaluation of the degree of wasting of the lean body mass and of the degree of current needs; (2) institution of a diet supplying what is missing and what is currently required, supplemented with enough protein, and distributed in at least three meals per day. This diet should be integrated with vitamins, minerals and iron; (3) use of

anabolic agents or a blend of the three substances we used. Irrespective of which medical treatment will be used, the closure of a wound will be impossible unless these steps are followed.

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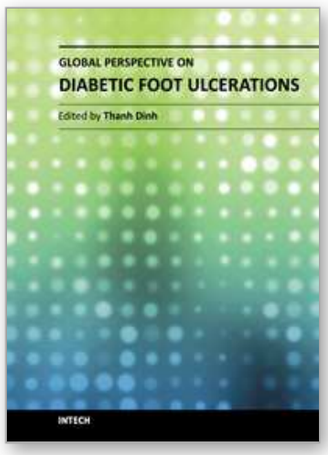
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Global Perspective on Diabetic Foot Ulcerations
Edited by Dr. Thanh Dinh

ISBN 978-953-307-727-7
Hard cover, 278 pages
Publisher InTech
Published online 09, December, 2011
Published in print edition December, 2011

Over the last decade, it is becoming increasingly clear that diabetes mellitus is a global epidemic. The influence of diabetes is most readily apparent in its manifestation in foot complications across cultures and continents. In this unique collaboration of global specialists, we examine the explosion of foot disease in locations that must quickly grapple with both mobilizing medical expertise and shaping public policy to best prevent and treat these serious complications. In other areas of the world where diabetic foot complications have unfortunately been all too common, diagnostic testing and advanced treatments have been developed in response. The bulk of this book is devoted to examining the newest developments in basic and clinical research on the diabetic foot. It is hoped that as our understanding of the pathophysiologic process expands, the devastating impact of diabetic foot complications can be minimized on a global scale.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Patrizio Tatti and Annabel Barber (2011). Nutritional Treatment of Diabetic Foot Ulcers - A Key to Success, Global Perspective on Diabetic Foot Ulcerations, Dr. Thanh Dinh (Ed.), ISBN: 978-953-307-727-7, InTech, Available from: http://www.intechopen.com/books/global-perspective-on-diabetic-foot-ulcerations/nutritional-treatment-of-diabetic-foot-ulcers-a-key-to-success

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