Diabetes & Metabolic Syndrome: Clinical Research & Reviews 8 (2014) 57–61

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Perspective

An integrated medical treatment for type-2 diabetes

Velio Bocci [a,*], Iacopo Zanardi [b], Maya S.P. Huijberts [c], Valter Travagli [b,**]

[a] Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Siena, Italy
[b] Department of Internal Medicine, Division of Endocrinology, Maastricht University Medical Centre (MUMC), Maastricht, The Netherlands
[c] Department of Physiology, University of Siena, Siena, Italy

ARTICLE INFO

Keywords:
Diabetes
Oxidative stress
Oxygen-ozonetherapy
Antioxidants
Nrf2 activation

ABSTRACT

This paper tries to emphasize two relevant concepts: the first is that type 2 diabetes is a chronic diseases characterized by both a dysmetabolism and a chronic oxidative stress. A variety of orthodox drugs are somewhat able to correct the metabolic alterations, but do not deal with the chronic inflammation. Consequently, as the validity of precisely treating blood with therapeutic ozone concentrations in restoring a redox homeostasis has been now demonstrated, the integration of ozone therapy appears essential for a rational treatment of type 2 diabetes. Such a combination may be able to reduce the diabetic epidemic.

Contents

1. Introduction

In 2000, with some approximation, it was estimated that there were 170 million people suffering from diabetes. This number has grown to 346 million people in 2012 and it has been supposed that in 2030 there will be 439 million diabetic patients [1]. If indeed about 6% of the world population will suffer from diabetes, by adding the huge number of patients affected by possibly concomitant chronic cardiovascular diseases, it will represent an unsustainable socioeconomic burden. Ironically, in spite of the prolongation of the life-span, an erroneous life style leads to such a high number of patients who will further unbalance the cost of medical expenses.

Diabetes mellitus can mainly manifest into three categories: Type 1-, gestational-, and type 2- diabetes. Type 1 diabetes mostly happens in children (about 10%) and for practical reasons it will be not discussed here. Gestational diabetes needs careful medical supervision throughout the pregnancy, but normally disappears after delivery. On the contrary, type 2 diabetes includes almost 90% of patients and tends to be progressive, unless an effective treatment is adopted. The progression of type 2 diabetes induces a multiform pathology complicated by a chronic oxidative stress. Careful dieting associated with moderate physical exercise and above all antidiabetic drugs have an important role in slowing down the progression of the disease. Medical treatment, though efficacious, does not always normalize the deranged metabolism. Moreover, the biochemical dysfunction is accompanied by a progressively worsening of a chronic oxidative stress, with complex anatomo-pathological lesions at the level of many organs. The concomitant use of oral antioxidants certainly is not harmful, but it is practically ineffective in normalizing the redox system. On the other hand, in the last decade it has been demonstrated that the Nrf2/Keap1 signalling pathway is the master system for cell defence against oxidative stress and, if properly activated, can resurrect the cellular redox balance at physiological levels [2–4].

* Corresponding author at: Emeritus Professor of Physiology at the Department of Physiology, University of Siena, Viale A. Moro 2, 53100, Italy. Tel.: +39 577 234226; fax: +39 577 234219.
** Corresponding author at: Chief of the Post-Graduate School of Hospital Pharmacy, University of Siena, Viale A. Moro, 2, 53100, Italy. Tel.: +39 577 234226; fax: +39 577 234219.
E-mail addresses: velio.bocci@unisi.it (V. Bocci), valter.travagli@unisi.it (V. Travagli).

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http://dx.doi.org/10.1016/j.dsx.2013.10.004

During the last few years we have clarified that precisely treating blood with therapeutic ozone concentrations induces the formation of two messengers such as hydrogen peroxide and alkenals [5]. The latter, especially 4-hydroxynonenal (4-HNE), is an electrophile able to inhibit the suppressive action of Keap1 allowing the translocation of Nrf2 into the nucleus and the binding to the Antioxidant Response Elements (ARE) [6,7]. Such a mechanism is optimally activated by ozone therapy, a complementary approach of which the biological and molecular aspects have been thoroughly evaluated during the last two decades [5]. In fact, both preclinical and clinical studies in diabetes as well as in chronic oxidative stress have shown its validity in reactivating the innate antioxidant system [8]. Consequently, the integration of orthodox medical treatment with this approach can normalize the redox system and it is likely to significantly reduce the diabetic dysfunctions.

1.1. Anatomo-biochemical alterations of type 2 diabetes

The first problem is usually referred to the hyperglycemia due either to the insulin receptor resistance or to a decreased insulin secretion [9]. As obesity frequently accompanies type 2 diabetes, the release of detrimental adipokines from adipose tissues further complicates the disease [10]. The following biochemical mechanisms are greatly responsible for the glucose-mediated vascular damage:

(a) Increased formation of advanced glycation end products (AGEs). Their development has been recognized as an important pathophysiological mechanism in the development of diabetic complications [11,12]. The Maillard reaction is a non-enzymatic glycosylation occurring when an α-aminogroup of the β-chain of haemoglobin reacts with a reducing sugar such as glucose. The reaction yields Schiff-base intermediates, which undergo the Amadori rearrangements to stable ketoamine derivatives. These compounds degrade into a variety of α-dicarbonyl compounds able to react with proteins forming irreversible AGEs which, taken up by cell receptors (RAGEs), stimulate the synthesis of proinflammatory cytokines such as IL-1 and TNF-α and of matrix proteins able to induce an irreversible damage. AGEs are detrimental for endothelial cells present in the corneal stroma and in the lens, accelerating cataract formation. Moreover, they particularly damage the vascular and neuronal system;
(b) activation of protein kinase C isoforms enhances the amount of diacylglycerol in vascular cells;
(c) the abnormally high glycemia is shunted into the hexosamine pathway leading to increased production of TGF-β1 and plasminogen activator inhibitor-1;
(d) an increased polyol pathway flux. Activation of aldose reductase leads to increased conversion of glucose to sorbitol with concomitant decrease in NADPH useful for regenerating oxidated GSH. The reduced GSH/GSSG ratio decreases the antioxidant defence. Moreover, a decrease of NO synthesis leads to enhanced platelet aggregation and vasoconstriction [13];
(e) type 2 diabetic patients often have infections due to immunological mediated acute phase reactions: experimental data have shown elevated levels of serum amyloid A, C-reactive protein and development of inflammatory responses [14,15]. Long-term type 2 diabetes frequently shows a decreased chemotaxis of neutrophils [16], an impaired monocyte adhesion to vascular endothelium [17] and a reduced phagocytic activity [18]. The increased levels of circulating and pathogenic immune complexes (IC) have been detected [19] and their deposition in the endothelium causes an inflammatory response by the activation of the complement cascade. In comparison to healthy controls, C1, C2, C3 and C4 proteins were significantly higher in type 2 diabetic patients [20] inducing the formation of micro- and macrovascular diseases.

The initial problem of type 2 diabetes is the hyperglycemia frequently due to insulin resistance, possibly combined to reduced insulin secretion. In obesity, there is a different production and release of adipokines in comparison to the release of adiponectin and leptin occurring in normal subjects. The release of resistin and of pro-inflammatory cytokines (IL-1; IL-6 and TNFα) from adipocytes, fibroblasts, macrophages and monocytes present in adipose tissue appears involved in mediating insulin resistance in peripheral tissues [10]. Needless to say that a careful control of glycemia and glycosilated haemoglobin with an appropriate and a fairly restricted diet associated with daily exercise is important. Otherwise, a diffused macrovascular disease can leads to the following complications:

(a) atherosclerosis can become evident with hypertension, myocardial infarction, stroke and limb vascular obstruction complicated with necrotic ulcers. Diabetic foot disease is frequently accompanied by polyneuropathy and infected foot ulcers [21];
(b) neuropathy may involve both the somatic and autonomic nervous system with neuromuscular dysfunction and wasting;
(c) diabetic nephropathy occurs in about 30% of patients and it may lead to end stage renal disease;
(d) diabetic retinopathy may cause blindness in the majority of patients.

1.2. Progression of type 2 diabetes is dominated by a chronic oxidative stress

Baynes [22] was one of the first to emphasize the role of a diffused oxidative stress. West [23] suggested a scheme indicating the interaction between hyperglycemia and the increased production of reactive oxygen species (ROS) such as $O_2^{\bullet}-$, H_2O_2, $^{\bullet}OH$, $ONOO^-$. An excessive consumption with a decreased synthesis of GSH leads to a lower GSH/GSSG ratio, which is a significant marker of oxidative stress. Another negative aspect is due to the AGE compounds binding to the endothelium and to the erythrocyte membrane favouring a worsening of the oxidative stress because the cellular innate molecular mechanism of restoring antioxidant enzymes (SOD, GSH-reductase and transferase, catalase, etc.), phase-2 enzymes and HO-1 is somewhat inhibited and incapable of neutralizing the excess of oxidants.

Orthodox medicine disposes of excellent drugs as antidiabetics, statin, antihypertensive and anticoagulants but their administration, although slowing down diabetes progression, cannot re-establish a normal redox system because some of these drugs are unable to reactivate the cellular antioxidant system. However, after two decades of intensive work, it is now possible to use a complementary system able to normalize the redox system [5,7]. The integration of this approach with orthodox medicine may indeed interrupt this vicious circle and can be very helpful to the patient.

1.3. The integration of orthodox drugs with ozone therapy

Nowadays, ozone therapy is used every day in most public hospitals in India, China, Russia and Cuba and in private clinics by many physicians, particularly in Germany. However, orthodox medicine disregards ozone therapy either owing to the lack of knowledge or simply by preconception based on the well-known