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Forum Review

The Expanding Role of Oxidative Stress, Renin Angiotensin System, and β-Cell Dysfunction in the Cardiometabolic Syndrome and Type 2 Diabetes Mellitus

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ABSTRACT

The incidence of obesity, cardiometabolic syndrome (CMS), and type 2 diabetes mellitus (DM2), as well as their devastating cardiovascular consequences, keep rising with increasing human and economical costs. For a long time, insulin resistance has been the main player in the pathogenesis and treatment of DM2, but every day more knowledge is gained about the central role of β-cell failure, not only in the appearance of hyperglycemia but also in the failure of the pharmacological therapy. β-Cell failure implies impairment of glucose-stimulated insulin secretion and loss of β-cell mass. Hyperglycemia, elevated circulating fatty acids, inadequate local activation of renin angiotensin system, and chronic low grade inflammation are conditions that coexist in the CMS and DM2 that turn out to be deleterious for the β-cell functioning and existance. Excessive oxidative stress secondary to increased production of reactive oxygen species and decreased availability of antioxidants is a possible common converging point of the multiple noxious stimuli. Activation of the NADPH oxidase complex secondary to angiotensin II stimulation is of interest, as its pharmacological blockade has beneficial effects. New knowledge about the intimate mechanisms of oxidative-stress induced β-cell failure will provide new therapeutic targets against CMS and DM2. *Antioxid. Redox Signal.* 9, 943–954.

INTRODUCTION

Obesity and type 2 diabetes mellitus (DM2) prevalence and incidence have reached epidemic proportions in both industrialized and nonindustrialized countries. According to the International Diabetes Federation, it is calculated that roughly 6% of the world's population is affected by diabetes mellitus, and ~97% of these patients are affected specifically by DM2. The estimated number of diabetics is expected to reach 221 million by the year 2010 (3), and 300 million in 2025 (114).

As expected, this epidemiologic explosion will impose a dramatic burden not only in terms of human suffering, but also on the health care systems worldwide. According to the American Diabetes Association, the cost of treating diabetic patients in the United States, with >12 million diagnosed diabetics, during the year 2002 alone was ~132 billion U.S. dollars, including direct costs of treating the disease, as well as costs attributable to management of DM2-related complications and increased prevalence of general medical conditions (2). Moreover, implications of the diabetic epidemic reach far beyond DM2, as they affect the occurrence of cardiovascular disease (CVD), which by itself is a leading cause of morbidity and mortality in industrialized societies. Not only the medical care cost of patients with DM2 is significantly greater in diabetics compared to the nondiabetics, but largely the excess cost is accounted for by management of CVD-related complications. Furthermore, costs attributable to DM2 increase well before the clinical diagnosis of the disease is made (69).

Of special concern is the rapidly increasing incidence and prevalence of DM2 in young populations. The early concept of children being mainly affected by type 1 diabetes mellitus (DM1) has been challenged over the last decades, and the occurrence of DM2 in children and adolescents is increasing

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alarmingly, as DM2 has been shown to account for as many as 50% of newly diagnosed cased of diabetes in urban areas of the United States (24). Epidemiologic studies have also demonstrated a 10-fold increase in the incidence of DM2 in pediatric and adolescent patients between the decades of 1980s and 1990s, a finding significantly related to presence of overweight and obesity (25). Indeed, in pediatric populations, overweight and obesity are leading risk factors for developing DM2, and both conditions follow similar epidemiologic trends (7). Worldwide, it is calculated that ~22 million children <5 years old meet criteria for overweight, and the increase of the condition in children over the last three decades exceeds 100% (84). Similar to the situation in adults, the trends vary according to ethnic background of the patients, and in the United States affect more commonly Mexican American adolescents and African Americans, compared to non-Hispanic white populations (36). Sadly, the presence of pediatric overweight or obesity is likely to persist in adulthood if no intervention is undertaken (95). Together, available evidence demonstrates that obesity, cardiometabolic syndrome (CMS), and DM2 epidemic is originated very early in life and under the influence of numerous factors. Strategies to control the impact of these conditions require the development of interventions targeting not only adult but young populations as well.

THE IMPORTANCE OF THE CARDIOMETABOLIC SYNDROME

The CMS, defined as a clustering of cardiovascular risk factors including hyperglycemia, obesity, hypertension (HTN), dyslipidemia, and albuminuria (Table 1), is one of the fastest growing conditions worldwide, affecting not only industrialized, but also nonindustrialized countries (29).

In the United States general population, the prevalence of the CMS was calculated to be ~22% in adult men and women from 1988 to 1994, according to data from the Third National Health and Nutrition Survey (NHANES III), considered to be one of the most representative samples of the United States population (75). Further analysis of the NHANES III cohort from 1999 to 2000, documented a prevalence of up to 34.5%. The prevalence of the CMS increases with age, and has been estimated to be ~43.5% in U.S. adults >50 years old (1). Importantly, using the newer International Diabetes Federation (IDF) criteria (Table 1), the prevalence of the syndrome reached 39%, with a higher prevalence in Mexican Americans, compared to other populations (28).

As previously discussed, epidemiologic studies also point toward a dramatic increase in the CMS frequency in children and adolescents. According to the NHANES survey, the prevalence of the CMS increased to 6.4% between 1999 and 2000, affecting approximately one third of overweight adolescents (23).

The reasons underlying the abovementioned epidemiologic dramatic increase in the incidence and prevalence of CMS and DM2 are largely related to the obesity epidemics. During the past 30 years, the prevalence of obesity in the United States has more than doubled (94), while excess body weight affects at least 65% of the adult population (27). These trends are mirrored by the rest of the world, according to the World Health Organization (WHO) (45).

In turn, even if the etiology of obesity is multifactorial and involves multiple genetic, biochemical, and metabolic factors, decreased physical activity, high caloric diets rich in saturated fats and carbohydrates do play a major role in weight gain (66).

The current importance of the concept of the CMS is not only its ability to recognize that cardiovascular risk factors tend to cluster, but also its capability to predict an increased frequency of CVD, stroke, DM2, and chronic kidney disease (CKD). Indeed, the CMS allows for early recognition of individuals and populations at higher risk for these complications, and for instituting early preventive as well as therapeutic strategies.

Table 1. Cardiometabolic Syndrome Definition Criteria

WORLD HEALTH ORGANIZATION (1998)	EUROPEAN GROUP FOR THE STUDY OF INSULIN RESISTANCE (EGIR) (1999)
Dysglycemia: fasting glucose ≥110 mg/dL or impaired glucose tolerance (>140 mg/dL or insulin resistance) AND two or more of the following: Dyslipidemia: triglycerides ≥150 mg/dL and/or HDL <35 mg/dL in men, <40 mg/dL in women Hypertension: BP >140/90 mm Hg Hypertension: BP ≥140/90 mm Hg and/or on medication Microalbuminuria: urinary albumin excretion >20 ig/min (>30 mg/g Creatinine)	Insulin resistance: Fasting hyperinsulinemia (>25%) AND two or more of the following: Dyslipidemia: triglycerides >170mg/dL or HDL <40 mg/dL Hypertension: BP >140/90 MM Hg Hypertension: BP ≥140/90 mm Hg and/or on medication Central obesity: waist circumference ≥94 cm in men, ≥80 cm in women Dysglycemia: fasting glucose ≥110 mg/dL
ADULT TREATMENT PANEL III (ATP III) (2001)	**ADULT TREATMENT PANEL III (ATP III) (2001)**
Three or more of the following: Central obesity: waist circumference ≥102 cm in men, ≥88 cm in women Dyslipidemia: triglycerides ≥150 mg/dL, HDL<40 mg/dL in women Hypertension: BP ≥135/85 mm Hg or on antihypertensive medication Fasting glucose >110 mg/dL	Central obesity: waist circumference ≥90 cm in men, ≥80 cm in women And TWO or more of the following: Dyslipidemia: triglycerides ≥150 mg/dL or on medication; or HDL <40 mg/dL in men, <50 mg/dL in women, or on medication Hypertension: SBP ≥130 mm Hg or DBP ≥85 mm Hg or on medication Dysglycemia: fasting glycemia ≥100 mg/dL

B-CELL DYSFUNCTION IN THE CMS AND DM2

DM2 accounts for >80% of all cases of diabetes mellitus worldwide. However, the condition is heterogeneous in nature, and specific genetic and autoimmune disorders including maturity-onset diabetes of the young (MODY) syndromes and latent adult-onset autoimmune diabetes (LADA) can account for ~5–10% cases diagnosed as DM2 (32). In these conditions, the defects leading to impaired glucose homeostasis are well characterized. However in the majority of type 2 diabetics, the cause of the disease is still poorly understood and subject to great debate despite impressive research available.

DM2 etiology includes genetic and environmental factors. Genetic contributions to DM2 are polygenic and require

abnormalities in multiple genes related to insulin sensitivity and/or insulin production, as well as environmental influences related to energy homeostasis through dietary and physical activity patterns. From a pathophysiological standpoint, the above mentioned factors convey impaired insulin sensitivity and impaired β-cell function, which finally result in hyperglycemia and DM2.

Insulin resistance has been the focus of considerable research and publications over the last decades, but the role of disturbances in the production and/or secretion of insulin is gaining mounting importance. The relative importance of insulin resistance versus β-cell dysfunction and insulinopenia are avidly studied worldwide, as well as their underlying mechanisms.

Studies performed in normoglycemic individuals genetically predisposed to DM2, including first degree relatives of type 2 diabetics, identical twins (discordant for DM2), normoglycemic women with history of gestational diabetes mellitus, strongly support genetically-mediated defects in β-cell function over insulin resistance as causes of DM2. Indeed, in these particular individuals more than half of the available studies support β-cell dysfunction rather than insulin resistance as the initial genetic abnormality (32). Caucasian patients with impaired glucose tolerance have insulin secretion dysfunction, when compared to individuals with normal glucose tolerance (104). In a recent clinical study by Van Haeften and coworkers, evidence of insulin secretion dysfunction was found also in individuals with impaired fasting glucose and glucose intolerance, as well as in type 2 diabetics. Insulin sensitivity was reduced more predominantly in advanced stages of DM2 (104).

In addition, it is generally accepted that insulin resistance is reversible at least to some extent through diet, weight loss, exercise, and insulin sensitizing pharmacologic agents, while defects in insulin production do not always follow this trend (9, 32). These observations point towards genetically determined abnormalities in insulin production and secretion in patients that develop DM2.

Finally, the concept of insulin resistance as an indispensable condition for the development of DM2 is also a matter of debate. Studies performed in European nonobese type 2 diabetics show β-cell dysfunction without associated insulin resistance, in contrast with obese DM2 participants (6). Similar reports have been published in black nonobese diabetic patients (10), as well as in Japanese adults with IGT (99). Collectively, these studies suggest that DM2 can develop in the absence of insulin resistance.

β-Cell dysfunction is an early event in the pathophysiology of DM2, as it has been estimated that >50–60% of β-cell insulin secretion capacity is lost when DM2 is clinically diagnosed (13). Indeed, a tightly regulated balance between insulin sensitivity and pancreatic secretion of insulin, as well as the production of glucose in the liver regulates blood glucose concentrations (78). To maintain homeostasis, if insulin sensitivity is reduced, β-cell must increase insulin output to maintain a constant glucose disposition (Fig. 1) (78). As opposed to insulin resistance, which is compensated for by an increase in the production of insulin, impaired β-cell dysfunction does not have a compensatory mechanism, thus leading to hyperglycemia (79). In addition,

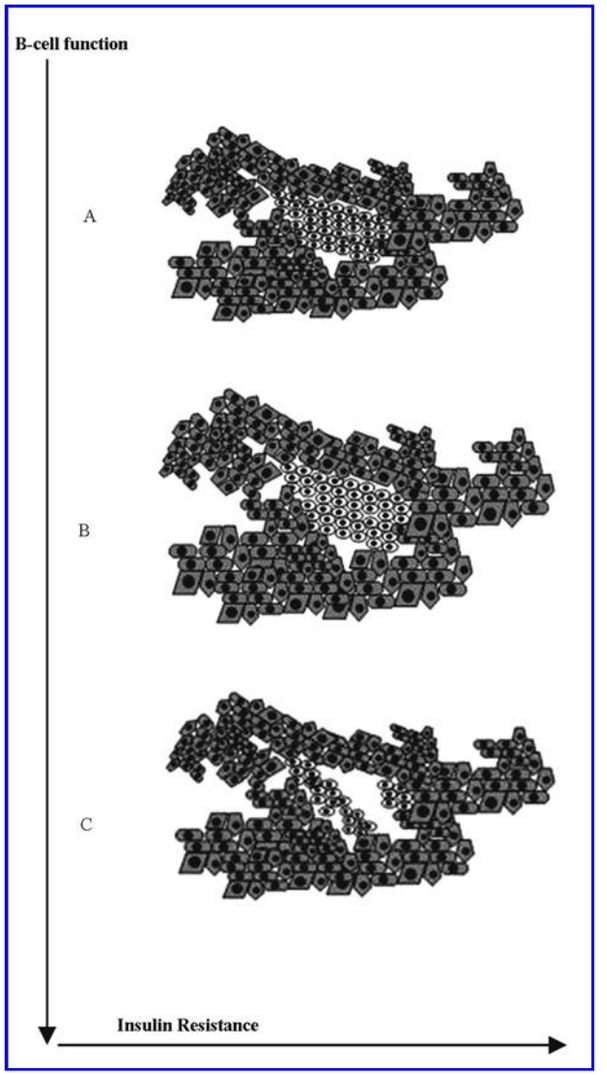

FIG. 1. The dynamic relationship between insulin sensitivity and insulin secretion. (**A**) Normal scenario. (**B**) In early stages, increased insulin resistance is compensated for by insulin secretion and beta-cell hyperplasia. (**C**) Impaired glucose tolerance and DM2 result from failure to compensate insulin resistance, caused by β-cell dysfunction and β-cell reduced mass.

even if measured absolute plasma levels of insulin are increased in early stages of DM2, available β-cells are unable to produce normoglycemic, which points towards an impaired secretory capability.

In rodent models it has been documented that single defects in the insulin action pathway induce hyperinsulinemia and β-cell hyperplasia instead of diabetes (12), and overt hyperglycemia only develops after significant insulin secretion deficiency is created (100).

The observed functional defects originating in the endocrine pancreas range from an early blunting of first phase of glucose-induced insulin response to disproportionate proinsulinemia in the presence of hyperglycemia, and basal

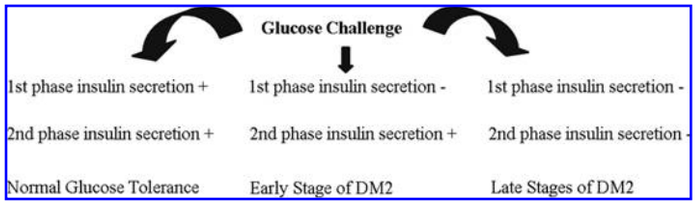

FIG. 2. Loss of glucose-induced insulin secretion. Normal scenario and progressive blunting of normal insulin secretion response in DM2. +, unaffected; –, decreased or blunted.

insulinopenia (Fig. 2) (78). After a glucose load, type 2 diabetics appear to have a decreased early (30 min) insulin release, which leads to more pronounced hyperglycemia compared to individuals with normal glucose tolerance. In early stages of DM2, the second late phase of secretion can be preserved due to the hyperglycemic stimulus, but eventually is also impaired in the course of the disease (77, 105). Also, acute insulin release stimulated by other nonglucose secretagogues, including arginine, secretin, sulfonylureas, and β-adrenergic agents, is impaired when values are corrected for the degree of hyperglycemia (34).

Other β-cell abnormalities observed in type 2 diabetics include an increased proportion of released proinsulin to insulin, both in basal and glucose-stimulated conditions, which could be accounted for by disturbances in the intracellular processing of insulin and hence β-cell dysfunction (46). Interestingly, release of proinsulin molecules is proportional to hyperglycemia and thus could be used as a surrogate of β-cell malfunction (82). Alternatively, an increased demand of insulin owing to hyperglycemia that leads to immature β-cell granules and secretion of insulin precursors can also be argued (46).

PANCREATIC ISLET AMYLOID IN DM2

Along with the above-mentioned β-cell abnormalities, specific morphologic changes observed in DM2 pancreas deserve special attention. Islet amyloid polypeptide (IAPP), a 37 amino acid peptide originally described by Opie in 1901 (73) and later characterized in the 1980s (107), is consistently found to be deposited within the pancreatic islets in >90% of type 2 diabetic patients (39). IAAP, or amylin, is co-localized and co-secreted when insulin is released from β-cells, in response to glucose and nonglucose stimulation (47), and is found to be reduced in DM2 patients.

IAPP is the main constituent of amyloid in the pancreas. These deposits are organized as dense and rigid meshworks of nonbranching fibrils with a diameter oscillating between 8 and 10 Angstrom (Å), and a core composed by polypeptide chains arranged in antiparallel β-pleated sheets (47). This orientation in turn yields extensive hydrogen bonds availability, and gives the typical cross-β x-ray diffraction pattern observed in light and EM images of amyloid (Figs. 3 and 4).

Human IAPP (hIAPP) is a normal product secreted by β-cell granules, and, just as insulin, is derived from a precursor peptide which is postranslationally processed by proteolyitic cleavage before being secreted as a mature protein (89). After its secretion, hIAPP plasma clearance—mainly through the kidneys—is slower compared to insulin, but comparable to C peptide.

IAPP appears to antagonize insulin in the modulation of carbohydrate metabolism in animal models, as its actions include suppression of insulin-induced glycogen production in skeletal muscle, as well as reduction of insulin-mediated glucose disposal (55, 93). An inhibitory effect on glucose-stimulated insulin secretion has also been noted in rats (21).

However, some of IAPP effects may be interpreted as beneficial; in rodent models IAPP delays gastric emptying, and by

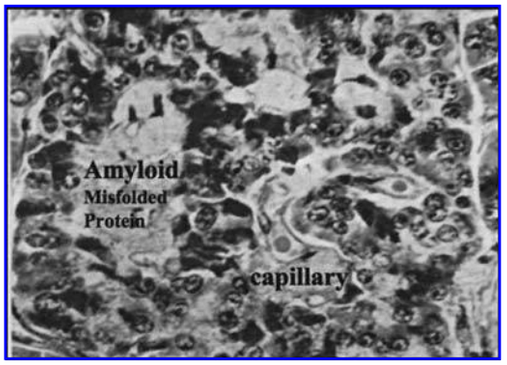

FIG. 3. Light microscopy appearance of amyloid in pancreatic tissue. Courtesy of M. R. Hayden, Research Professor of Medicine, Department of Internal Medicine, Division of Endocrinology, University of Missouri-Columbia.

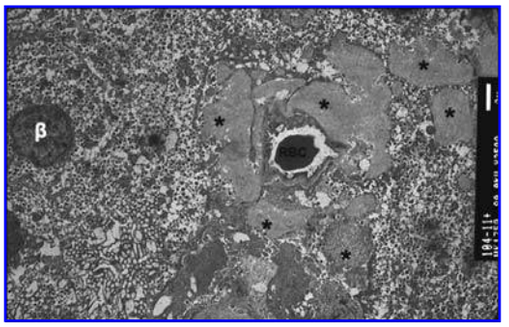

FIG. 4. Electron microscopy appearance of amyloid with pericapillary distribution. Courtesy of M. R. Hayden, Research Professor of Medicine, Department of Internal Medicine, Division of Endocrinology, University of Missouri-Columbia.

this mechanism slows glucose absorption, with a theoretical helpful effect on carbohydrate and insulin homeostasis, through reduction of postprandial hyperglycemia (111). A role for IAPP in the regulation of appetite has also been suggested, as injection of amylin, either systemically or in hypothalamus, induces anorexia in rats (16,17).

In humans, amyloid deposits in the pancreas are composed of amylin as well as other proteins, such as apolipoprotein E, serum amyloid P component, and heparan sulfate. In physiologic conditions, IAPP remains in a monomeric soluble nonfibrillar form, which does not induce amyloid formation. Concentrations of C peptide, zinc, calcium, and pH conditions in the β-cell secretory granules (18, 108), as well as the formation of stable complexes with insulin, appear to prevent formation of the β-sheets structures that are necessary for amyloidogenesis (44).

On the other hand, in a disturbed endocrine pancreas *milieu*, as occurs in chronic hyperglycemia, increased levels of circulating fatty acids (FA), inflammation, and oxidative stress create favorable conditions for deposition of amyloid. Amyloidogenesis in the islet leading to fibril formation and cytotoxicity involves altered processing of IAPP in β-cells. This results in secretion of misfolded IAPP from β-cell secretory granules and formation of β-pleated sheets structures that in turn assemble and result in oligomeric soluble aggregates that are cytotoxic (43). As recently reviewed, β-cell dysfunction is also necessary for fibril formation and final amyloid extracellular deposition in the pancreas (41).

The role of amyloid as an active participant involved in the development of DM2 versus a consequence of the pathophysiologic processes that lead to DM2 is a matter of debate and research. Available data regarding the role of IAPP in development of insulin resistance and/or insulin secretion dysfunction have yielded variable results. The development of specific transgenic rodent models expressing hIAPP has greatly contributed to better understand the role of amyloid in DM2 (20).

As stated previously, IAPP deposits can be detected in up to 90% of DM2 patients and is diffusely distributed throughout the islet early in the course of DM2 (26), but cannot account for the remaining cases of DM2, in which they are not observed. In addition, amyloid deposits exists in diabetic humans, cats, and nonhuman primates, but not in rodents, despite having a clinical course similar to human DM2.

In addition, early experimental studies in mice have not shown disturbances in glucose homeostasis in animals expressing hIAPP (109). Also in transgenic mice, IAPP has not been related to significant hyperglycemia or hyperinsulinemia (40).

Islet amyloidosis has been linked to reduced β-cell mass and decreased insulin secretion capacity, as insulin-requiring patients appear to have larger islet amyloid deposits (39). Autopsy-based studies in humans have documented concomitantly amyloid deposits and decreased β-cell number in DM2 patients, suggesting a causal role (109). Indeed, the cytotoxic effect of soluble hIAPP oligomers is well known, and the suggested mechanism appears to be apoptosis secondary to stimulation of specific apoptosis-related genes (113).

A recent paper by Meier *et al*. analyzed the role of hIAPP fibril inhibition on β-cell apoptosis in transgenic rats (67). The use of rifampin, an inhibitor of hIAPP fibril formation—but not of toxic hIAPP oligomers development—did not prevent β-cells from undergoing apoptosis in conditions of increased hIAPP, either by direct application or overexpression. This underscores the importance of early hIAPP oligomers in the development of apoptosis and reduction of β-cell mass, as opposed to more mature forms of amyloid. Finally, amyloid-induced cytotoxicity appears to be mediated at least partially by increased oxidative stress, as experimental studies have documented, in addition to increased apoptosis, time- and concentration-dependent induction of oxidative stress-related genes, including cox-2 and IkappaB-alpha (37,103).

ROLE OF B-CELL MASS IN PATHOPHYSIOLOGY OF ALTERED GLUCOSE TOLERANCE AND DM2

A tightly regulated balance between proliferation and cell death modulates β-cell mass. Acute hyperglycemia in nondiabetic humans and in rodent models has been shown to result in early expansion of β-cell mass (76). However, chronic hyperglycemia leads to decreased proliferation of pancreatic β-cells (22). Recent studies in humans have found an increased β-cell mass in obese nondiabetic patients through neogenesis, while in obese individuals with glucose intolerance β-cell mass is reduced by roughly 40%. In the same study, in lean type 2 diabetic subjects the reduction was estimated at 41%, whereas in obese diabetics it was ~63%. According to the researchers, apoptosis was the main mechanism responsible, and was increased 10-fold in obese diabetics. No significant differences in the rates of neogenesis were found among the participants, suggesting that β-cell loss was accounted for by increased apoptosis (13).

The failure of the human pancreas to adapt to conditions of increased metabolic requirements, such as the CMS, is related to genetic susceptibility as previously discussed, and to a deleterious effect of altered carbohydrate metabolism. In human pancreatic cells, hyperglycemia can result in increased production of interleukin 1β (IL-1β) in the islets (62), which in turn can upregulate the expression of the Fas receptor, a known apoptotic mediator (63). Fas upregulation mediated by hyperglycemia can be activated upon reduction in the expression of the caspase-8 inhibitor FLIP, also leading to apoptosis (61, 62).

OXIDATIVE STRESS-MEDIATED INJURY AND B-CELL RESPONSE

Reactive oxidative species can interact with proteins, lipids, and nucleic acids, and cause damage to the β-cell. Since ROS are part of the normal intracellular environment, control mechanisms have been developed to buffer these effects, creating a delicate balance between oxidation and endogenous antioxidant machinery. Disruption of this equilibrium in the CMS and DM2 leads to predominance of oxidative stress.

Recent studies suggest that ROS are involved in cell death through the inhibition of phosphatases of the *Jun N-terminal* kinase (JNK) pathway, perpetuating its activation with

subsequently cytochrome c release and caspase 3 cleavage (48). Hyperglycemia can also cause β-cell apoptosis through nuclear factor (κB activation, caspase activation and ROS production.

As discussed above, β-cell IL-1-β production is also enhanced by hyperglycemic conditions, activating several pathways that convey in apoptosis (65).

As an adaptative response to onset on insulin resistance, β-cells undergo hyperplasia and overproduction of insulin (81). However, β-cell mass expansion is only a transitory response to increased demand conditions that later would be insufficient to maintain normoglycemia, leading to impaired glucose tolerance and later to DM2 (13). This transient expansion of β-cells can be achieved through β cell replication, hypertrophy of existent cells, and neogenesis (11), but unfortunately, it is not clear yet which mechanisms are relevant in postnatal human pancreas.

Signals that promote compensatory β-cell hyperplasia include glucose, free fatty acids, glucagon-like peptide-1 (GLP-1), insulin, and insulin growth factors (IGF) (81). Insulin receptor substrate-2 (IRS-2) is an intracellular tyrosine kinase substrate involved in downstream signaling of insulin and insulin-like growth factors. IRS-2 has a central role in the control of β-cell survival and its blockade has been related to increased apoptosis (83). After IRS-2 activation, the phosphatidylinositol-3-kinase/protein kinase-B pathway is activated, leading to β-cell survival and replication, via mechanisms that result in nuclear exclusion of the transcription factor Foxo1 (106). Foxo1 otherwise negatively regulates β-cell proliferation through PDX-1 repression (70).

In addition, similar mechanisms to the ones accountable for muscle and liver insulin resistance can have a role in β cell death. Hyperglycemia, increased free fatty acids, and cytokines/inflammation can cause serine/threonine residues phosphorylation of IRS-2 with subsequently blockade of its anti-apoptotic signaling cascade and degradation through an ubiquitin/proteosomal pathway (83).

EFFECT OF GLUCOTOXICITY AND LIPOTOXICITY

The interrelationship between lipids and carbohydrates metabolism, representing a reciprocal interaction of fatty acid and glucose oxidation is very well known (92). It is also established that chronic hyperglycemia and increased FA, both features of DM2 and the CMS, lead to β-cell dysfunction and impaired insulin secretion (87).

Glucotoxicity is characterized by prolonged, and potentially irreversible impairment of glucose-stimulated insulin secretion (GSIS) in conditions of chronic hyperglycemia. On the other hand, acute and prolonged hyperglycemia leads to transient and reversible disturbances in insulin secretion caused by β-cell exhaustion and depletion of intracellular insulin stores (49). Mechanisms implicated in glucotoxicity include reduced activity of key β-cell transcription factors such as the pancreatic-duodenum homeobox-1 (PDX-1) and RIPE 3b1, and reciprocally increased expression of transcriptional repressors of the insulin gene, such as CCAT/enhancer-binding protein β (72, 90).

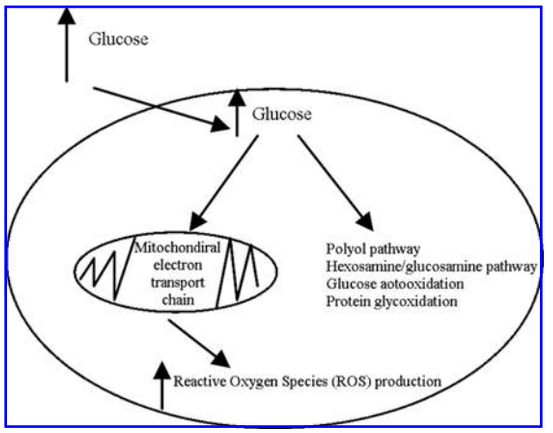

FIG. 5. Intracellular metabolic pathways of glucose leading to production of reactive oxygen species (ROS).

Oxidative stress has also been implicated as an active player in the development of glucotoxicity. Indeed, chronic hyperglycemia results in increased production of reactive oxygen species (ROS) and generation of advanced glycation end products (AGEs), which in turn are associated with reduced transcription of genes involved in insulin production (97). The reversibility of these changes by antioxidants such as aminoguanidine and *N*-acetyl-L-cysteine suggests an active role of oxidative stress (98).

Chronic hyperglycemia leads to increased glucose oxidation through anaerobic glycolysis, derivation of the excess glucose towards ROS-producing pathways including glucosamine generation, protein glycosilation/oxidation through Schiff reactions and glucose autooxidation (Fig. 5) (86). The overproduction of ROS eventually overcomes endogenous antioxidant systems including catalase, superoxide dismutase, and glutathione peroxidase, which have been found to be relatively deficient in the pancreatic islets, compared to other tissues (64, 87). As opposed to other tissues, the ability of the pancreas to adapt to conditions of increased metabolic demand and oxidative-stress-mediated injury makes it particularly vulnerable, resulting in β-cell dysfunction and apoptosis.

On the other hand, chronically elevated levels of FA in plasma and in the pancreatic islets impair β-cell function. Toxic effects of increased FA appear to require hyperglycemia. Indeed, in conditions of normoglycemia FA do not affect cultured β-cell insulin secretory capacity in experimental conditions. However, when hyperglycemia develops, insulin production does significantly decline (42). Studies in rodent models of DM2 demonstrate that isolated control of hyperglycemia reduces triglyceride accumulation in pancreatic islets and preserve insulin production. On the other hand, isolated control of hyperlipidemia without glycemic reduction does not produce the same effects on the β-cells, suggesting that chronic hyperglycemia is required for development of lipotoxicity (35). In addition, experimental studies suggest that low density lipoproteins (LDL), and very low density lipoproteins (VLDL) exert

proapoptotic actions on β-cells, an action that appears to be prevented by high density lipoproteins (HDL) (88).

In hyperglycemic conditions, FA inhibit insulin gene expression, and the transcription factor islet duodenum homeobox-1 (IDX-1) (33). Prolonged hyperlipidemia in addition leads to inhibition of carnitine palmitoyl transferase 1, the limiting enzyme that regulates entry of FA inside the mitochondria for subsequent β oxidation. Also in the presence of hyperglycemia, this leads to cytosolic accumulation of long-chain fatty acyls CoA (LC-CoA), which in turn have been associated with impaired β-cell function (80). Mechanisms underlying these effects include modulation of the expression of protein kinase C, the ATP-sensitive potassium channel, as well as uncoupling protein-2 genes (15). Again, excessive production of ROS is implicated, as demonstrated *in vitro* that islets FA can increased ROS generation (52).

Elevated free fatty acids can have adverse functional and pro-apoptotic effects on the endocrine pancreas. Exposure of isolated human islets to high concentrations of oleate and palmitate may alter GSIS, mainly secondary to altered intracellular glucose metabolism. Additionally, apoptosis enhancement, is at least partially explained by caspase pathway activation and parallels a mark reduction in Bcl-2 mRNA (59).

In humans, it has been documented that type 2 diabetics exhibit increased markers of oxidative stress and lipid peroxidation such as 8-hydroxy-deoxyguanine, 4-hydroxy-2-nonenal proteins, 8-epi-prostaglandin F_2, and hydroperoxides, while their levels of glutathione are diminished when compared to control subjects (85).

Dysfunctional adipose tissue found in obese diabetic patients and in people affected by CMS is characterized by a chronic low grade inflammatory status, and increased production of adipokynes, including leptin, TNF-α, and IL-6. Leptin has been shown to have proinflammatory cytokine-like activity, and induces β-cell apoptosis *in vitro* by activating IL-1β and inhibiting IL-1 receptor antagonist (62).

One of the main mediators of inflammation in obesity, the nuclear factor κB (NF-κB), has been related to β-cell dysfunction/apoptosis through increased IL-1β, an effect that is reversible by salicylate and thiazolidinediones (TZD) (51, 112).

THE RENIN ANGIOTENSIN SYSTEM AND OXIDATIVE STRESS INTERPLAY IN THE DEVELOPMENT OF B-CELL FAILURE

The endocrine pancreas is not only exposed to systemic but also to locally produced components of the renin angiotensin system (RAS); and in conditions such as the CMS, obesity and DM2, RAS activity is inappropriately upregulated.

In rodents, the existence of angiotensinogen, angiotensin converting enzyme (ACE), and angiotensin II receptors 1 and 2 (AT1R and AT2R) has been documented in pancreatic islets. (54, 56, 57). In human pancreas tissue, renin precursors and AT1R have been found in β-cells, as well as in endothelial cells of the pancreatic vasculature (96).

The physiological role of the pancreatic RAS appears to involve islet blood flow regulation, an effect capable of affecting insulin secretion. In mouse islets, increasing concentrations of angiotensin II (Ang II) impaired in a dose-dependent manner glucose-stimulated insulin secretion. This effect that was reversed in this study by losartan (14, 54).

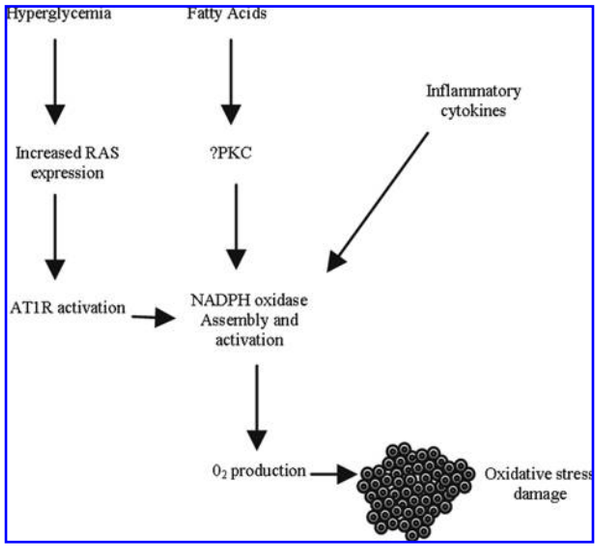

FIG. 6. Increased reactive oxygen species (ROS) production mediated through increased activity of rennin angiotensin system (RAS) and nicotinamide adenine dinucleotide phosphate, reduced (NADPH) oxidase activity. PKC, protein kinase C; AT1R, angiotensin Type 1 receptor.

Hyperglycemia *per se* can activate RAS in human islets. As reported by Lupi and coworkers, isolated human islets exposed to high glucose concentrations increased their expression angiotensinogen, ACE, and AT1R. In addition, a significant increase in oxidative stress, and a marked decrease in insulin secretion capability were documented. The increased oxidative stress was related with increased expression on NADPH oxidase subunit p22 and phosphorylation of PKC β2, suggesting a mechanism by which RAS triggers production of ROS and oxidative stress (Fig. 6). Under high glucose concentrations, angiotensin converting enzymes inhibitors (ACEI) exerted beneficial effects on β-cells regarding insulin production and oxidative stress (60).

The role of the NADPH oxidase deserves special mention. NADPH oxidase is a multienzymatic electron transfer complex which uses NADPH as substrate with the final production of superoxide. The complex consists of five subunits: membrane-bound components gp91 and p22, and cytosolic fractions p47, p67, and G protein Rac.

Classically described in cells with phagocytic capacity such as neutrophils and monocytes, (8) and more recently in the vasculature (58), the role of NADPH oxidase in oxidative stress in the pancreas is now also a field of active research.

Oliveira *et al.* demonstrated the presence of NAPDH oxidase subunits in rat pancreas. Using real time polymerase chain reaction (RT-PCR) analysis and Western blot, the presence of $gp91^{PHOX}$, $p22^{PHOX}$, $p47^{PHOX}$, and $p67^{PHOX}$ in the pancreatic islets was documented. The existence of cytosolic $p47^{PHOX}$ in the β cells was recognized by immunohistochemistry.

Interestingly, under hyperglycemic conditions this subunit was translocated to the plasma membrane, with a simultaneous increase in production of superoxide (71).

In addition to glucose, palmitate and inflammatory cytokines can stimulate NADPH oxidase-mediated ROS production (68). These experimental conditions replicate the *in vivo* environment that can be found in DM2 and in the CMS where elevated glucose, FA, and inflammatory cytokines are a typical finding.

Finally, recent reports demonstrate a beneficial effect of RAS blockade with angiotensin II receptor blockers (ARBs) on pancreatic production and secretion of insulin. Obesity-induced DM2 in *db/db* mice has been related to β-cell dysfunction, likely via activation of pancreatic RAS and upregulation of AT1R present in the pancreas. ARBs increased both insulin production and secretion. Furthermore, hyperglycemia, glucose intolerance, and onset of diabetes were also delayed, without affecting insulin resistance markers (19). These data support the role for pancreatic RAS in the development of β-cell dysfunction, and provide important information about the mechanisms implicated in the beneficial effects of RAS blockade on glucose metabolism.

ISLET FIBROSIS

The role of islet fibrosis in the pathogenesis of DM2 is of special interest, as progressive fibrosis of the pancreas has been documented in animal models of obesity and diabetes. This process seems to involve the increased production of transforming growth factor β 1 (TGF-β 1) (110), a classic profibrotic cytokine, and pancreatic stellate cells (PSC) activation (4).

RAS activation is a player in the development of islet pancreatic fibrosis. Hyperglycemic conditions activate PSC with a parallel increased production of Ang II (50), and RAS blockade through candesartan or ramiprilat suppress the expression of extracellular matrix proteins in cultured rat PSC (50). More recently, not only high glucose concentrations but also high insulin concentrations were shown to activate PSC, probably through MAPK pathway activation (38). In a rodent diabetic model, db/db mice, treatment with candersartan resulted in improvement in glucose tolerance test with a reported decreased of pancreatic oxidative stress markers, intra-islet fibrotic changes, and an amelioration of disruptive ultrastructural changes (91).

The above findings support the idea that inadequate activation of the renin angiotensin system has also deleterious profibrotic effects on the pancreatic islet and this may contributes to β cell failure.

ROLE OF MITOCHONDRIAL AND ENDOPLASMIC RETICULUM DYSFUNCTION

Mitochondrial production of superoxide anions is an inevitable effect of the respiratory chain; by themselves superoxide anions are potent oxidative agents but additionally they can also react with nitric oxide generating peroxinitrate, which is another powerful oxidant.

Within the mitochondria, different strategies counterbalance the effects of ROS. Superoxide anions are converted to hydrogen peroxide (H_2O_2) by manganese-superoxide dismutase (MnSOD), and later H_2O_2 is cleared from the mitochondria by glutathione peroxidase (31). Additionally superoxide dismutase isozyme and cytochrome *c* are also available for the control of oxidative burst.

Available data suggest a poor capacity of β cell endogenous antioxidant mechanisms to adapt to increased oxidative stress activity. In an animal model, Tiedge *et al.* showed a lower expression in rat pancreatic islets of superoxide dismutase, catalase, and glutathione peroxidase when compared to liver cells; additionally in this experiment islets were not able to raise their antioxidant enzyme expression in hyperglycemic conditions (101).

Regarding the role of FA, some authors believe that free fatty acids through additional production of reducing equivalents can increase mitochondrial production of ROS and subsequently oxidative stress (30).

Finally, disturbances in the endoplasmic reticulum (ER) related to development of altered glucose homeostasis are an emerging field of research. Impairment of normal protein folding in the ER as part of the ER stress, can redirect β-cells to apoptotic pathways (5) and has also been implicated in the development of insulin resistance (74).

CONCLUSIONS AND PERSPECTIVES

The epidemic of obesity, CMS, and DM2 that affects both industrialized and nonindustrialized countries demands the development of novel strategies to uncover the mechanisms that lead to insulin resistance, β-cell dysfunction, and finally to atherogenesis and cardiovascular disease. In the pathogenesis of CMS and DM2, the role of impaired insulin sensitivity has received a great deal of attention both from experimental and clinical standpoints. However, less is known about the mechanisms that lead to impaired insulin production and secretion. As β-cell dysfunction to control insulin resistance and compensatory hyperinsulinemia is essential for the development of clinical DM2, the mechanisms of this failure are being increasingly explored. Insulin production and secretion are affected by numerous pathologic processes, among which inappropriate activation of the RAS, oxidative stress-related changes, and amyloid deposition appear to be of paramount importance. These early pathophysiologic events lead to increased apoptosis, reduced β-cell mass, and impairment of insulin production and insulin secretion, which in turn impair carbohydrates and lipid homeostasis. A vicious circle is also created, in which lipotoxicity and glucotoxicity further exacerbate insulin resistance and β-cell dysfunction.

Available evidence points towards genetic as well as environmental causes of ROS mediated-β-cell dysfunction. Indeed, conditions present in the CMS, such as chronic dysglycemia, hyperlipidemia, insulin resistance, chronic inflammation, and RAS—both local and systemic—display variable cross-talk mechanisms, and have been related to increased production of ROS. A better understanding of the underlying mechanisms actively provides the basis for the development of therapeutic strategies, including the rationale for a tighter glucose and lipidic

TABLE 2. RENIN ANGIOTENSIN SYSTEM (RAS) BLOCKADE AND TYPE 2 DIABETES MELLITUS PREVENTION

Trial	*Study population*	*Mean follow up time (years)*	*RAS blockade strategy*	*Primary outcome*	*Relative Risk*
CAPPP (1999)	*Hypertensives*	*6.1*	*ACEI*	*Composite of myocardial infarction, stroke, and other cardiovascular deaths.*	*0.79 (0.67-0.94)*
HOPE (2000)	*Vascular disease or diabetes + one other cardiovascular risk factor + low ejection fraction or heart failure*	*5*	*ACE*	*Composite of myocardial infarction, stroke, and other cardiovascular deaths.*	*0.66 (0.51-0.85)*
DREAM (2006)	No cardiovascular disease	*3*	*ACEI*	*Development of diabetes or death*	0.91 (0.81–1.03) Non significant
ALLHAT (2003)	*Hypertension and at least 1 other CHD risk factor*	*4.9*	*ACEI*	*Combined fatal CHD or nonfatal myocardial infarction*	*0.70 (0.56–0.86)*
CHARM (2003)	*Heart failure*	*3.2*	*ARB*	All-cause mortality	0.78 (0.64–0.96)
VALUE (2004)	*Hypertensive patients at high cardiovascular risk*	*4.2*	*ARB*	*Composite of cardiac mortality and morbidity*	*0.77 (0.69-0.86)*

control, blockade of the RAS, as well as anti-inflammatory and antioxidant therapies. Blockade of the RAS through angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers has proven in large studies to improve individual components of the CMS beyond the effect that could be attributable to HTN control, as well as a beneficial effect on glucose homeostasis and prevention of DM2 (53). The recent DREAM trial did not replicate these findings in terms of DM2 prevention, but did show a positive effect of ACEI in glucose homeostasis and return to normoglycemic (102) (Table 2). Newer strategies directed to preventing β-cell dysfunction associated with increased oxidative stress are actively being developed, with the aim of controlling not only CMS, DM2, but also cardiovascular disease, and the burden these conditions impose on public health.

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ABBREVIATIONS

AGEs, advanced glycation end products; ACE, angiotensin converting enzyme; Ang II, angiotensin II, AT1R and AT2R, angiotensin II receptor 1 and 2, ACEI, angiotensin converting enzymes inhibitors; ARBs, angiotensin II receptor blockers; CMS, cardiometabolic syndrome; CVD, cardiovascular disease; CKD, chronic kidney disease; IDX-1, factor islet duodenum homeobox-1; GLP-1, glucagon-like peptide-1; hIAPP, human IAPP; HTN, hypertension; IGF, insulin growth factors; IDF, International Diabetes Federation; IAPP, islet amyloid polypeptide; LADA, latent adult-onset autoimmune diabetes; LC-CoA, long chain fatty acyls CoA; MnSOD, manganese superoxide dismutase; MODY, maturity onset diabetes of the young; RAS, renin angiotensin system; RT—PCR, real time polymerase chain reaction; ROS, reactive oxygen species; DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; NHANES III, Third National Health and Nutrition Survey; TGF-β 1, transforming growth factor β 1; WHO, World Health Organization.

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