Islet Amyloid, Metabolic Syndrome, and the Natural Progressive History of Type 2 Diabetes Mellitus

Melvin R Hayden

Department of Family and Community Medicine. University of Missouri School of Medicine. Columbia, Missouri, USA

Abstract

The presence of amyloid within the islet of the pancreas may be one of the best kept secrets in clinical medicine and translation of this century old finding may help to better understand the progressive nature of type 2 diabetes mellitus. Insulin resistance, metabolic syndrome, and type 2 diabetes mellitus are associated with multiple metabolic toxicities which result in an elevated tension of redox stress within the islet. Redox stress is associated with damage to proteins, lipids, and nucleic acids which may have a profound affect upon the structure and function of the islet. Earlier diagnosis at the stage of impaired glucose tolerance (prediabetes) and intervention may have a positive outcome on stabilization of the vulnerable islet and beta cell as well as the multiple diabetic complications. The natural history and a shift in the treatment paradigm of type 2 diabetes mellitus is explored as a result of these century old findings.

Background and Historical Perspective

It has now been a century (1901) since Eugene L Opie first described the presence of hyalinosis within the islets of the pancreas in patients with hyperglycemia [1, 2].
This hyalinosis has subsequently been identified as amyloid (Figure 1) and in 1987 two separate investigators in separate laboratories determined it consisted of the monomeric unit - islet amyloid polypeptide (IAPP) or amylin - which when aggregates and polymerizes forms amylin derived islet amyloid (ADIA) [3, 4, 5]. Amylin is a 37 amino acid polypeptide with an amyloidogenic portion between amino acids number 20 and 29 [6]. It is capable of forming amyloid due to a unique amino acid sequence with its associated secondary structural conformation that only occurs naturally in cats and monkeys which develop type 2 diabetes mellitus (T2DM) spontaneously similar to humans [6]. Amylin parallels insulin's synthesis, secretion, and excretion and may be considered insulin's fraternal twin of the mother beta cell [7]. The two may act in a synergistic manner in helping to understand insulin resistance, metabolic syndrome, and the progressive nature of T2DM [8].


Figure 1. Amyloid highlighted within a single islet. ADIA forms between beta cells and between beta cells and endothelial cells creating a diffusion barrier (space occupying lesion) resulting in a secretory defect and an absorptive defect surrounding islet capillaries.

Insulin Resistance and the Metabolic Syndrome

Insulin resistance describes the condition whereby there is a resistance to insulin mediated glucose uptake by cells and is central to the clustering of multiple metabolic abnormalities and clinical syndromes. The clustering phenomenon was first described by Kylin in 1923 when he described the clustering of three clinical syndromes: hypertension, hyperglycemia, and hyperuricemia [9]. In 1936 Himsworth [10] noted that a large number of diabetic patients were insulin insensitive. Yalow *et al.* in 1965 [11] were first to discover an insulin assay and reported that insulin resistance was a condition in which insulin does not produce the same glucose lowering effects seen in insulin-sensitive individuals. These concepts were rejuvenated and immortalized by Reaven in 1988 given as the Banting lecture [12]. The clustering phenomenon has gone by many names since Reaven first described the metabolic and clinical associations of the many names of Syndrome X [13, 14].

Additionally, there are at least a dozen factors that link clinical suspicions to the metabolic syndrome (Table 1). Factors and findings in this syndrome occur together all to frequently to be considered a coincidence and there are common underlying factors that may explain
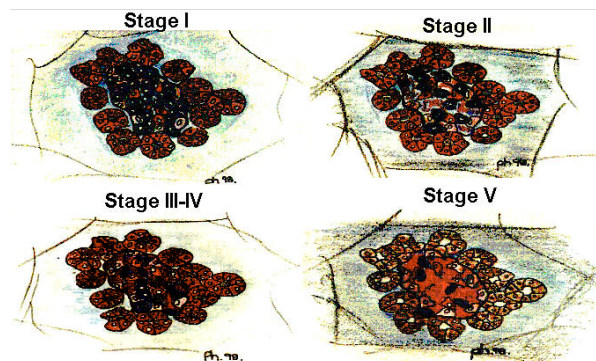
Figure 2. This figure demonstrates the ADIA changes within the islet: The five stages in the natural history of T2DM. Stages III and IV are incorporated together in the newly named "prediabetic" stage.

this coexistence. Namely, the well documented hyperinsulinemia story and the more recent hyperamylinemia and amylin derived islet amyloid story [13, 14, 15].

In 1999, the World Health Organization chose a unifying definition for this syndrome of many names and elected to use the term metabolic syndrome rather than the insulin resistance syndrome because they felt it was not well established that insulin resistance was the cause of all components of the syndrome [16]. Each of us probably have our own "pet term" that we commonly use for this clustering phenomenon but henceforth the appropriate term shall be referred to as the metabolic syndrome with no disrespect to any

Table 1. Factors that link clinical suspicions to insulin resistance, metabolic syndrome, and a proclivity to develop T2DM.

1. Strong family history of diabetes mellitus.
2. High risk ethnic background (Aboriginal, Asian, Pacific Islander, Hispanic, African American, Native American Indian).
3. Obesity (visceral, omental). Phenotypic changes of abdominal obesity: waist/hip ratio equal or greater than 1 in males and equal or greater than 0.8 in females.
4. Gestational diabetes.
5. Macrosomia.
6. Multiparity.
7. Polycystic ovary syndrome (PCOS).
8. Impaired glucose tolerance. Two-hour postprandial blood sugar ranging from 140 to 199 mg/dL after 75 gram OGTT
9. Impaired fasting glucose : 110-125mg/dL.
10. Ageing.
11. Hypertension.
12. Dyslipidemia. The lipid triad (increased VLDL, triglycerides, small dense LDL. Decreased HDL).

previous naming of this clustering phenomenon.

Metabolic syndrome affects approximately 47 million or greater Americans [17]. It is currently estimated that only 20% of patients with insulin resistance and hyperinsulinemia-hyperamylinemia develop T2DM, while the remaining 80% are able to compensate at least for a period of time through the process of beta cell expansion, hypertrophy, and hyperplasia (utilizing the replicative pool of periductal cells) [18, 19].

Natural History of Type 2 Diabetes Mellitus

There are at least three diabetogenic factors: polygenic, environmental, and the endogenous histological structural defects associated with ADIA which interacts and contributes to the development and the progressive nature of T2DM (Figure 2) [13, 14, 15]. In addition to the contemporary widely accepted two hallmark features of insulin resistance and beta cell dysfunction there is a tight association of T2DM with obesity and sedentary life style.

Definition: "T2DM is a heterogeneous, multifactorial, polygenic disease characterized by a defect in insulin's secretion (the beta cell secretory defect) and action (insulin resistance)".

T2DM may be viewed as a continuum consisting of five stages: latent stage, transition stage, impaired glucose tolerance stage, impaired fasting glucose stage, and the overt stage with three subdivisions mild, moderate, and severe based on the degrees of abnormality of HbA1c and insulin levels reflecting the degree of beta cell dysfunction or failure *i.e.* mild, moderate, severe, and complete.

Unless there is an intervention, T2DM is characterized by a progressive nature and there is "a point of no return" wherein this devastating disease seems to progress regardless of the treatment provided as demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS) [20]. For this very reason a change in the treatment paradigm should be considered and thus an emphasis will be placed on the "impaired glucose tolerance stage - Stage III". Delaying treatment until there is chronic hyperglycemia places the patient at great risk for the development of not only overt T2DM but also the even more morbid devastating events associated with the development of an accelerated prediabetic and diabetic atherosclerosis (atheroscleropathy) and its inherent 2-4 fold increase in coronary artery disease and up to a 6 fold increase in congestive heart failure which is so costly in terms of morbidity, mortality, quality of life issues, and the financial burden to society. Two important quotes regarding the current situation (the double jeopardy of T2DM and atheroscleropathy) are relevant:

• The impact of cardiovascular disease on mortality and morbidity in people with diabetes has been known for years. Approximately two-thirds of people with diabetes die from cardiovascular disease (coronary heart disease, stroke, and other vascular diseases) [21];

• Diabetes must take its place alongside the other major risk factors as important causes of cardiovascular disease. In fact, from the point of view of cardiovascular medicine, it may be appropriate to say: "diabetes is a cardiovascular disease" [22].

T2DM and the metabolic syndrome have finally gained their proper respect in the 2001 National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III) guidelines as T2DM is now considered a coronary risk equivalent and metabolic syndrome is included in the multiple risk factors for the development of atheroscleropathy and cardiovascular disease [23].

Stages in the Natural History of Type 2 Diabetes Mellitus

Stage I of the Continuum (The Latent Stage)

The latent stage may be identified by a strong clinical suspicion (Table 1) or the presence of at least one of the other markers of disease such as hypertension, coronary artery disease, dyslipidemia of the lipid triad (elevated VLDL cholesterol-triglycerides, decreased HDL cholesterol, elevated small dense atherogenic LDL cholesterol) associated with the metabolic syndrome. Histologically, amyloid is probably insignificant at this stage. The HbA1c is not elevated and glucose tolerance is normal with associated early elevations of insulin and amylin levels. A high level of clinical suspicion helps to identify this stage. Lifestyle changes are strongly encouraged both diet and exercise.

Stage II of the Continuum (The Silent Transition Stage)

The transition stage marks the beginning of structural changes within the islet with increasing amyloid aggregation and deposition. This results in a diffusion barrier (a space occupying lesion) and is the time when there is considerable damage to the beta cell due to the direct toxic effects of intermediate sized toxic amyloid particles (ISTAPs) [24]. Walsh *et al.* found that naturally secreted oligomers (similar to ISTAPs) of amyloid beta protein inhibited hippocampal long-term potentiation in vivo signifying that the oligomers or intermediate sized amyloid particles are toxic to cells similar to the findings of Janson *et al.* and Walsh *et al.* [24, 25]. These toxic effects result in apoptosis of the beta cells and for a certain period of time the more primordial ductal cells of the exocrine pancreas (replicative pool) can replace the damaged apoptotic beta cells and continue the compensatory hyperinsulinemia and hyperamylinemia [18] which cause further beta cell damage and contributes to the diffusion barrier. During this time there is development of a basement membrane absorptive defect. ADIA has a proclivity to bind to the heparan sulfate proteoglycan (perlecan) within basement membranes of intra islet capillaries. Thus, basement membranes surrounding islet capillaries are thickened and develop an absorptive barrier which aids in understanding the decreased first phase insulin secretory response through an absorptive defect.

The totality of beta cell function remains intact until there is approximately 50% damage or dysfunction of beta cells or disruption of absorptive capability. Histologically, amyloid would be in the 25-50% stage (Figure 2). Insulin and amylin levels are increased and HbA1c and glucose tolerance would be normal. This stage is silent and represents a very active disease process without clinical signs or symptoms. The high index of clinical suspicion and associated clinical findings allow clinicians to be alerted to this stage similar to stage I. The time interval from suspecting stage I and II is important as time is not on the patients side unless there has been major changes in lifestyle in regards to diet and exercise.

Stage III of the Continuum (Prediabetes Stage): The Impaired Glucose Tolerance (IGT) Stage

The impaired glucose tolerance (IGT) stage is characterized by an abnormal response to a glucose challenge. The 75 gram oral glucose tolerance test is characterized by a normal fasting glucose with an abnormal 2-hour postprandial glucose in the range of 140-199 mg/dL. In March 2002 the Department of Health and Human Services (DHHS) and the American Diabetes Association (ADA) have provided a new term for this stage: "prediabetes". The term IGT and impaired fasting glucose (IFG) may be termed "prediabetes".

This stage represents a histological change within the islet of approximately 50-75% of ADIA involvement of islet architecture (Figure 2) or associated beta cell dysfunction.

Insulin and amylin levels are increased. Glucose tolerance is now abnormal with HbA1c remaining normal. This stage is extremely important as it is the stage wherein we can identify a large number of patients who will progress to overt stage V unless there is a significant intervention. At this time the clinician can obtain objective laboratory evidence that the transition stage is approaching "a point of no return". It is known that 50% of patients with IGT will progress to overt (stage V) T2DM within ten years [26, 27, 28] unless there is aggressive intervention ("aggressive" life style changes in diet and exercise or institution of medication such as the insulin sensitizers-thiazolidinediones, metformin or the alpha glucosidase inhibitors as these medications will improve non fasting and postprandial glucotoxicity without elevating endogenous insulin or amylin). If this stage is left unattended the natural history of T2DM is progressive. If the patient is non-compliant then this allows the clinician to instruct for careful follow up and monitoring of blood sugars both fasting and 2 hour post challenge. Additionally, Tuomilehto *et al.* recently found from the Diabetes Epidemiology Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study that the two hour post glucose concentrations are better predictors of mortality than the fasting glucose alone [29].

Stage IV of the Continuum (Prediabetes Stage): The Impaired Fasting Glucose (IFG) Stage

The fasting glucose now becomes abnormal due to a progressive global insulin resistance with the amount of insulin remaining inadequate to compensate for increasing hepatic insulin resistance resulting in excess gluconeogenesis and free fatty acids within the liver resulting in elevations of the fasting glucose but not yet to a diagnostic range for overt diabetes [30]. This stage is associated with a fasting blood glucose of 110-125 mg/dL. Insulin resistance is more global and the insulin and amylin levels remain elevated.

Histologically, amyloid would be in the 75% range (Figure 2). HbA1c levels would still be in the normal range and glucose tolerance would be abnormal.

Stage V of the Continuum (Overt T2DM Stage)

This stage is marked by either an abnormal fasting glucose equal to or greater than 126 mg/dL or a postprandial or random blood glucose equal to, or greater than, 200 mg/dL. The histological representation would be between 75-100% involvement of ADIA at this stage (Figure 2).

Stage Va: HbA1c ranging from 6.2 to 7.5%. Insulin resistance: moderate. Insulin levels increased or normal.

Stage Vb: HbA1c ranging from 7.6 to 10.0%. Insulin resistance: moderate/severe. Insulin levels decreasing.

Stage Vc: HbA1c greater than 10.0%. Insulin resistance: severe. Insulin levels markedly decreased to absent (Table 2, Figure 3) [30].
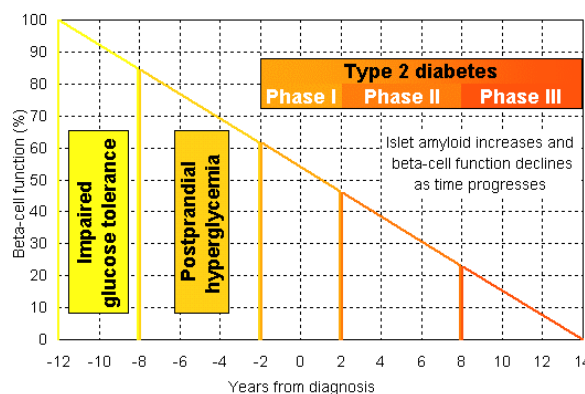
Figure 3. At the time of diagnosis of T2DM patients already have a 50% reduction in beta cell function. As one moves through the various stages-phases there is a progressive loss of beta cell function while concurrently there is increased deposition of amylin derived islet amyloid. If treatment were started at an earlier stage in the natural history of T2DM (Stage III: impaired glucose tolerance or "prediabetes") in a manner to control elevated glucose levels without elevating endogenous insulin or the monomeric substrate amylin then it may be possible to halt the progressive nature of T2DM. (Redrawn from Lebovitz HE [31]).

Table 2. The five stages of T2DM: the natural progressive history of T2DM.

I. LATENT STAGE: *[EARLY]*

Insulin Resistance:
- Genetic Component
- Environmental component. Modifiable: obesity/sedentary life style. Nonmodifiable: ageing.

Beta Cell Defect: (Dysfunction)
- Genetic .... Abnormal processing, storage or secretion.
- Intracellular/extracellular amylin fibril toxicity. Abnormal processing, storage or secretion.

Intra-Islet Endothelial Absorptive Defect:
- Heparan sulfate proteoglycan (HSPG) PERLECAN of the capillary endothelial cells avidly attracts amylin (IAPP) and the islet amyloid forms an envelope around the capillary. This is in addition to the increase in the basement membrane associated with the pseudohypoxia (associated with glucotoxicity) and the redox stress within the capillary.

II. TRANSITION STAGE: *[MIDDLE]*

Persistent Hyperinsulinemia

Persistent Hyperamylanemia
- Continued remodeling of the endocrine pancreas (amyloid).
- Beta cell displacement, dysfunction, mass reduction and diffusion barrier.

III. IGT STAGE (Impaired Glucose Tolerance): *[LATE]* "Pre-diabetes" Human Health Services (HHS) and American Diabetes Association (ADA) term.
[Start treatment at this time]
[Diagnose earlier: rejuvenation of the 2 hour glucose tolerance blood sugar 140-199 mg/dL]
- Increased insulin resistance [Feeds forward] > Glucotoxicity [Feeds forward] > Insulin resistance [Feeds forward] > Glucotoxicity: creating a vicious cycle.
- Islet amyloid. Increasing beta cell defect. Loss of beta cell mass with displacement. (Remodeling of islet architecture including extracellular matrix). Beta cell loss centrally.

IV. IFG STAGE (Impaired Fasting Glucose): *[LATER]* "Pre-diabetes" Human Health Services (HHS) and American Diabetes Association (ADA) term.
[Blood sugar ranging 110-126 mg/dL]
[Impaired hepatic glucose production]
- Increasing global insulin resistance (hepatic) with subsequent gluconeogenesis. Feeding forward in the vicious cycle to accelerate insulin resistance globally.

V. OVERT STAGE: *[TOO LATE]*
[50% loss of beta cell function]
Va, Vb, Vc. Phases I, II, III: mild, moderate/severe, complete. Use medications that do not increase insulin or amylin. Use combination therapy. Start treatment at stage III-IV (IGT-IFG).
- Paradigm Shift. Start treatment at the earlier stage of IGT.

Stages Va, Vb, and Vc are comparable to phases I, II, and III in Lebovitz's graph (Figure 3) [31, 32]. These stages are not meant to be rigid as the development of T2DM operates over a continuum and is capable of regression until the patient has reached a "point of no return": beta cell failure. It is important to note that in the graph (Figure 3) there is a 50% reduction in beta cell function at the time of diagnosis of overt T2DM.

The old saying that "time is on your side" does not hold true in the natural history of T2DM. In this disease and the associated

macrovascular disease the "clock starts ticking" prior to the diagnosis of hyperglycemia and overt T2DM [33]. There is a period of time that may last 5-10 years wherein the metabolic syndrome may be in play, thus, accelerating micro/macrovascular disease and it is widely accepted that aging is a known risk factor for the development of both macrovascular disease and T2DM. At the time of diagnosis of T2DM at least one fourth (or greater) of patients may have developed macrovascular complications [34]. Furthermore, at the time of T2DM diagnosis more than 50% of patients have existing or pre-existing coronary heart disease. This means every other new patient will be affected with this specific macrovascular disease [35]. Global risk reduction is of utmost importance in the T2DM patients as they have a risk equivalent equal to those patients who have previously had a myocardial infarction. Therefore our goal should be secondary prevention in risk reduction (global risk reduction) for all patients with T2DM (Table 3) [35]. Mortality in T2DM is associated primarily with atheroscleropathy.

T2DM is now considered to be a cardiovascular risk equivalent and the National Cholesterol Education Program (NCEP) ATP III guidelines point to aggressive treatment as well as the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI guidelines) and the National High Blood Pressure Education Program (NHBPEP) [36]. Grant recently reported that hypercholesterolemia, and hypertension were not managed or screened-for as aggressively as hyperglycemia [37]. Additionally, McFarlane *et al.* [38] and Sowers and Reed [36] were able to show in urban academic centers that cardiovascular risk factors in patients with diabetes and hypertension obtained the following goals: HbA1c less than 7: 26.7%; blood pressure of 130/85 mmHg: 26.7%; LDL cholesterol of less than 100 mg/dL: 35.5%; antiplatelet therapy: 45.6%. Only 3.2% of patients met the combined ADA goal for blood pressure, LDL cholesterol, and HbA(1c).

Redox Stress and Amyloid Formation

There is a tremendous amount of redox stress - the process of generating un-paired electrons, reactive oxygen species (ROS), oxygen free radicals (toxic oxygen) by the process of reduction or oxidation - within the islets and the arterial vessel wall of the insulin resistant, metabolic syndrome, and T2DM patient [13, 14]. ROS contribute to and are a result of advanced glycosylation endproducts (AGE) formation. This glycation and glycoxidation process modifies proteins,

Table 3. The RAAS acronym for the prevention and treatment of remodeling of the arterial vessel wall in atherosclerosis and stabilization of the vulnerable pancreatic islet.

R	Reductase inhibitors (HMG-CoA). Decreasing modified LDL cholesterol, i.e. oxidized, acetylated LDL cholesterol. Improving endothelial cell dysfunction. Thus, decreasing the oxidative stress to the arterial vessel wall and the islet. <u>Redox stress reduction.</u>
A	ACEi-prils. ARBS-sartans. Both inhibiting the effect of angiotensin-II locally as well as systemically. Affecting the hemodynamic stress through their antihypertensive effect as well as the deleterious effects of angiotensin II on cells at the local level - injurious stimuli. Decreasing the A-FLIGHT toxicities. Plus the direct/indirect antioxidant effect within the islet and the arterial vessel wall. <u>Redox stress reduction.</u>
	Aspirin antiplatelet, anti-inflammatory effect.
A	Aggressive control of diabetes. Decreasing modified LDL cholesterol, i.e. glycated LDL cholesterol. Improving endothelial cell dysfunction. Also decreasing glucose toxicity and the redox stress to the intima and pancreatic islet. <u>Redox stress reduction.</u>
S	Statins. Improving plaque stability (pleiotropic effects) independent of cholesterol lowering. Improving endothelial cell dysfunction and preventing the angiogenesis associated with arterial vascular remodeling which destabilizes the unstable atherosclerotic plaque. Plus, the direct/indirect antioxidant anti-inflammatory effects within the islet and the arterial vessel wall promoting stabilization of the unstable, vulnerable islet and the arterial vessel wall. <u>Redox stress reduction</u> [13, 14, 15].

lipids, and nucleic acids and results not only in damage to the islet and islet proteins but also greatly accelerates the process of atheroscleropathy within the arterial vessel wall. Redox stress is silent but results in a vulnerable islet prone to remodeling with the aggregation and polymerization of ADIA which adds to the progressive nature of this disease. Once ADIA has formed it is extremely resistant to the proteolytic enzymes within the extra cellular matrix. It seems paradoxical that ADIA deposition does not induce a chronic inflammatory response within the islet. Badman *et al.* and de Koning *et al.* were able to demonstrate that ADIA did not induce an inflammatory state within the islets and even though ADIA was internalized by macrophages it resisted proteolytic degradation [39, 40]. However, Opie in 1901 and 1910 was able to show a mononuclear inflammatory reaction in the exocrine portion of the pancreas with associated ADIA [1, 2].

It is important to place a quote by Badman *et al.* and de Koning *et al.* since we are discussing the progressive nature of T2DM: "Islet amyloidosis is progressive, apparently irreversible and is associated with destruction of insulin-secreting cells".

Amyloid deposits (AL amyloid in multiple myeloma) have been shown to regress with the use of ^{123}I-labeled serum amyloid P component scintigraphically when the disease state producing the monomeric unit is placed in remission so this provides a great hope for the future that the same will be true for ADIA in T2DM [41, 42].

There are multiple toxicities associated with insulin resistance, metabolic syndrome and T2DM. In an effort to categorize these toxicities the following mnemonic was created: A-FLIGHT toxicities [13, 14, 15]. Each of these toxicities are associated with the production of ROS and produce an unstable environment within the islet that can be compared to a violent lightning storm within the vulnerable islet. The damaging effects of unpaired electrons re-pairing creates a damaging effect to proteins, lipids, and nucleic acids. The ROS may cause an unfolding of the native secondary structure of

amylin [13, 14]. Once this compact folded native amylin is unfolded it then becomes possible (due to the amyloidogenic nature of amino acids 20-29) for the beta pleated sheet conformation to realign into a newly formed secondary conformational antiparallel crossed beta pleated sheet structure: ADIA [13, 14]. These monomeric units undergo a prolific free radical polymerization due to the presence of ROS. Thus, ROS may not only contribute the unfolding of the native amylin structure allowing it to refold into antiparallel crossed beta pleated sheets but also allow for the rapid polymerization into mature islet amyloid. If we can decrease the substrates of the A-FLIGHT toxicities, and thus decrease the ROS, we may be able to have a positive effect on the progressive nature of amyloid formation and subsequently have a positive effect on the progressive natural history of T2DM [13, 14, 15].

Currently, we have available newer medications (alpha glucosidase inhibitors, metformin, thiazolidinediones, the newer glinide analogs repaglinide and netaglinide, and soon the inhaled form of insulin Exubera™ and the oral buccally absorbed insulin spray Oralin™) which will have a positive effect on each of these toxicities [43, 44, 45]. Specifically, we can decrease the glucotoxicity without elevating endogenous insulin or its fraternal twin: the amyloidogenic native substrate amylin. Also we can utilize the RAAS acronym (Table 3) to decrease the redox stress and the ROS produced by the A-FLIGHT toxicities of insulin resistance, metabolic syndrome, and T2DM [13, 14]. Recently, the angiotensin converting enzyme inhibitor ramipril (Heart Outcomes Prevention Evaluation, HOPE study), the 3 hydroxy-3methylglutaryl-coenzyme A (HMGCoA) reductase inhibitor pravastatin (West of Scotland Coronary Prevention study, WOSCOPs), metformin (Diabetes Prevention Project, DPP), and the angiotensin II receptor antagonist (angiotensin receptor blocker: ARB) losartan (Losartan Intervention For Endpoint reduction in hypertension study, LIFE study) have been shown to reduce the relative risk of

developing T2DM by 34%, 30%, 31%, and 25%, respectively (Table 3) [46, 47, 48, 49, 50, 51].

Conclusion

We should strongly consider rejuvenating the two-hour 75 gram oral glucose tolerance test (2hOGTT) which will allow clinicians to diagnose the impaired glucose tolerance stage III (blood sugars: 140-199 mg/dL) at an earlier stage in the natural history of T2DM.

In order to identify those who will be more likely to progress to the stage V (overt T2DM; Table 2) we can utilize the 2hOGTT for stress testing those patients considered at high risk for development of stage V (overt T2DM; Table 1) just as we currently use the exercise and pharmacological stress testing for those suspected of having coronary heart disease.

For those who feel the inconvenience and cost of the 2-hour post glucose challenge are prohibitive a new "clinical model" was recently described by Stern *et al.* [52]. This clinical model which includes the clinical variables of age, sex, fasting glucose, body mass index, systolic blood pressure, HDL-cholesterol, family history, and high risk ethnic background was used to compare results of predicting the probability of developing T2DM over a 7.5 year follow up study. So in the future we may be able to use this clinical model to calculate the probability of developing overt stage V T2DM from the clinical history and laboratory values we are accustomed to using similar to using the Framingham risk calculation in the NCEP ATP III guidelines. This model was shown to be of equal value and even superior to predicting the onset of T2DM when compared to the 75 gram 2hOGTT to determine impaired glucose tolerance. Aggressive changes in life style (weight reduction and exercise) as employed in the diabetes prevention program which revealed a 58% reduction in the development of overt T2DM are clearly recommended [49].

Consideration for intervening with drug therapy with newer medications to prevent or slow the development of glucotoxicity with its associated multiple complicating diabetic opathies. and being aggressive in treating patients to those HbA1c levels known to be protective (HbA1c of 7% or less). The American College of Endocrinology (ACE) consensus statement on guidelines for glycemic control white paper has recently recommended newer goals of HbA1c levels to 6.5% being careful to avoid hypoglycemia especially in the elderly [53].

Also, employ newer medications that lower glucose and HbA1c values without elevating endogenous insulin or amylin. By lowering the amyloidogenic substrate amylin (in addition to the other substrates of the A-FLIGHT toxicities) we may be able to slow or prevent the progressive ADIA deposition within the islet and preserve beta cell function.

Be prepared to use these newer medications not only alone but also in combination therapy in order to achieve the desired HbA1c levels.

Consider using the medications in the RAAS acronym (Table 3) known to decrease the excess redox stress with a positive effect on the multiple A-FLIGHT toxicities associated with insulin resistance, metabolic syndrome, and overt T2DM [13, 14, 15].

By following this paradigm shift in the diagnosis, treatment, and prevention of the progressive nature of the natural history of T2DM we may be able to save the vulnerable islet, and prevent progressive ADIA deposition.

We are dealing with a disease of epidemic proportion in the United States and globally.

In the US there are 17 million people with diabetes and 90% (15.3 million) have T2DM. A review of four autopsy studies (two in the US, one in Germany, and one in Japan) revealed an average of 70% of T2DM patients have islet amyloid by light microscopy. This would correspond to an excess of 10 million patients with T2DM having positive amyloid staining (Congo red) with light microscopy.

Obviously, the presence of ADIA is huge and is felt to play a significant role in the remodeling of the endocrine pancreas as well

as the natural progressive history of T2DM [13, 14, 15].

Translating a century old finding may allow us to not only better understand the progressive nature of T2DM but also have a greater opportunity to have a positive affect on the natural progressive history of this malicious, chronic debilitating disease.

This is especially important in light of the current exponential growth globally of T2DM not only in our aging population but also in our adolescent youth [54].

In summary, we can become enhanced "EDUCATORS" for our at risk T2DM patients.

1. **E**arlier **D**iagnosis. Earlier intervention with life style modifications and drug therapy.

2. **U**se of newer medications to decrease glucotoxicity without elevating endogenous insulin or the amyloidogenic amylin.

3. **C**ombination therapy.

4. **A**ggressive **T**reatment to obtain the desired blood pressure, LDL-Cholesterol, and HbA1c levels known to be protective of the multiple complicating diabetic **O**pathies.

5. Use of those medication in the **R**AAS acronym to **R**educe **R**edox stress.

6. **S**ave**, S**tabilize, and preserve the beta cell and the vulnerable pancreatic islet.

Currently, we have available the technology and pharmacology to achieve these goals in order to have a positive effect on the horrendous cost (both quality of life issues and financial) to our society both at home and abroad.

Abbreviations 2hOGTT: two-hour 75 gram oral glucose tolerance test; ACE: American College of Endocrinology; ADA: American Diabetes Association; ADIA: amylin derived islet amyloid; AGE: advanced glycosylation endproducts; ARB: angiotensin receptor blocker; DECODE: Diabetes Epidemiology Collaborative analysis Of Diagnostic criteria in Europe; DHHS: Department of Health and Human Services; DPP: Diabetes Prevention Project; HMGCoA: 3 hydroxy-3methylglutaryl-coenzyme A; HOPE: Heart Outcomes Prevention Evaluation; HSPG: heparan sulfate proteoglycan; IAPP: islet amyloid polypeptide; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; ISTAPs: intermediate sized toxic amyloid particles; JNC: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LIFE study: Losartan Intervention For Endpoint reduction in hypertension study; NCEP: National Cholesterol Education Program; NHBPEP: National High Blood Pressure Education Program; ROS: reactive oxygen species; T2DM: type 2 diabetes mellitus; WOSCOPs: West of Scotland Coronary Prevention study

Correspondence
Melvin R Hayden
Department of Family and Community Medicine
University of Missouri School of Medicine
P.O. Box 1140
Lk. Rd. 5-87
Camdenton, Missouri
65020 USA
Phone: +1-573.346.3019
E-mail address: mrh29@usmo.com

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