ARTIGO ORIGINAL

Nutrology and type 2 diabetes: Nutrient pathophysiology and the transition from health to disease

Nutrologia e diabetes tipo 2: Fisiopatologia dos nutrientes e a transição da saúde à doença

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ABSTRACT

From a Nutrology point of view, type 2 diabetes is a multi-factorial form of clinical "malnutrition" resulting from the intake of an imbalanced diet in combination with adverse environmental conditions and in the presence of predisposing genetic factors. In this review article, we present evidence of a close association between clinical obesity in a specific genetic background as the pillars of the process underlying the development of type 2 diabetes. We review the basics of the energy balance and the role of fat storage and body distribution in the pathogenesis of insulin resistance. We describe some molecular aspects of nutrients under normal physiology and during the metabolic and hormonal abnormalities that accompany type 2 diabetes. We conclude with a brief discussion of the principles behind popular dietary recommendations aimed at preventing the full development of diabetes mellitus and its complications.

Keywords: Type 2 Diabetes, Nutrient Patho-physiology; Genetics and Obesity

INTRODUCTION

Nutrology is a new medical sub-specialty recognized in Brazil that deals with the role of food nutrients in health and disease. Medical Nutrology also encompasses the clinical relevance of nutrients in the process of diagnosis, treatment and prevention of "nutritional diseases". Type 2 diabetes mellitus, obesity, dyslipidemias, osteoporosis, hypertension, atherosclerosis, some cancers, mineral and vitamin deficiencies are some examples of human ailments that carry either primary or secondary nutrological disorders. During the course of these medical conditions, there are characteristic derangements in nutrients intake and metabolism, which affect the whole body, and in our view these should be addressed by the specialists in Medical Nutrology. In this article we will focus our attention on type 2 diabetes with an emphasis on the nutrient pathophysiology and the transition from health to disease.

From a Nutrology point of view, type 2 diabetes is a multi-factorial form of clinical "malnutrition" resulting from the intake of an imbalanced diet in combination with adverse environmental conditions and in the presence of predisposing genetic factors. Current estimates indicate that there are approximately 150 million patients suffering from type 2 diabetes worldwide and, the World Health Organization has projected the prevalence of the disease will increase to nearly 366 million people worldwide in the year 2030. Most of this increase is expected to take place in India, China, and in North and South America (1– 3). It is important to point out that in South America, Brazil, where an indigenous population who has been cultured and integrated lately by living nearby "modern communities" and consuming the local population food, as a substitute for their previous "jungle diet", the presence of obesity and diabetes has been shown to be significant (Dutra de Oliveira, personal communication). These observations highlight the fundamental role that inadequate nutrient

consumption and environmental factors play in uncovering the individual genetic predisposition, thus facilitating the clinical development of type 2 diabetes. These alarming data are paralleled by a coincident epidemic of obesity, commonly defined as an excess body fat as measured by Body Mass Index (BMI), which is an oversimplification since from a Nutrology viewpoint obesity is considered a more complex and multi-factorial syndrome of nutrient derangements and is not limited to the presence of "excess body fat". There is no question however that the presence of excess body fat stores, referred to as obesity has been detected within the same time frame and pretty much in the same geographical locations where type 2 diabetes is most prevalent. Although the evidence that increasing body weight and fat accumulation overtime tends to be accompanied by hormonal and metabolic stress with the development of significant insulin resistance and compensatory hyperinsulinemia is unequivocal, the single presence of obesity cannot create a state of diabetes. The number of people who are considered obese is known to be three times greater than those who carry the diagnosis of type 2 diabetes in the U.S. (4), suggesting that only 1/3 of all obese individuals at risk develop diabetes. A closer analysis of these populations reveals that diabetes will develop almost exclusively in those overweight individuals who belong to families with a predisposing genetic profile. Thus, the combination of obesity, nutrients/diet and other environmental factors superimposed on the "right" genetic profile is necessary for the full clinical manifestation of type 2 diabetes.

The natural history of type 2 diabetes mellitus, summarized in **Figure 1** derives from numerous longitudinal studies including high risk families, minorities and the Pima Indians and residents of Southwestern region of the United States (**5**). Clinically the first sign of diabetes is elevated plasma glucose in the postprandial period followed then by fasting hyperglycemia. Presumably, there is an inherited degree of insulin resistance in pre-disposed individuals and this is made worse and further enhanced by environmental factors, such as a sedentary lifestyle and the consumption of excess calories, unbalanced diets and harmful nutrients. All obese subjects will develop an acquired insulin resistance, but those with no genetic predisposition usually compensate the defect by secreting sufficient hormone so as to avoid the hyperglycemia. In contrast, however, in predisposed individuals the compensatory elevation in circulating insulin cannot overcome the state of insulin resistance, which reaches a maximum just before the diagnosis of diabetes is confirmed. The reason why the plasma glucose concentration remains within the normal range during the pre-diabetes period is because the pancreas compensates with insulin over-secretion, albeit inappropriate for the degree of cellular insulin resistance, hyperinsulinemia delays temporarily the appearance of hyperglycemia. The critical change that occurs at the time of diagnosis, which differentiates the obese subjects who will and will not develop diabetes, is a sharp decline in insulin secretion in individuals genetically predisposed. Type 2 diabetes is clinically evident only at the stage when beta-cell function is exhausted, which does not occur in obese subjects who do not have the genetic imprint to develop diabetes. Despite the fact that more than 100 genes have been identified to date in association with some phenotypic characteristic of type 2 diabetes, these can only explain 5-10% of all cases and therefore we are still far away from elucidating the genetics of diabetes.

In order to alter the natural history of the disease to prevent and delay the full development and progression of type 2 diabetes substantial modifications are needed in the offending environmental factors. These include changing the quality and the quantity of nutrient intake, balancing dietary intake, stimulating regular exercise and physical activity, and if necessary, utilizing pharmacological agents, which improve insulin sensitivity and/or preserve pancreatic insulin secretion. The implementation of these critical steps requires knowledge of some fundamental basic concepts surrounding the distribution and regulation of body fuel homeostasis in health and disease.

Energy Balance: Intake vs. Expenditure

It is well known that energy intake and expenditure are highly influenced by environmental and societal factors, as well as by the genetic makeup and individual choices. Energy expenditure can be essentially summarized in three categories: the resting or basal metabolic rate that fuels vital body functions, the thermic effect of food intake, inherit to the act of eating and digesting foodstuff, and a third category, which is variable and encompasses physical activity. On the opposite side of the equation, energy or caloric intake derived from three essential nutrients, fat, carbohydrate and proteins, which are consumed in varying amounts in each diet according to the availability of products and cultural habits. Obesity simply results from an imbalance between energy intake and expenditure over time. As an example, the North American diet today contains many highly palatable, calorically dense foods that, in combination with the sedentary lifestyle characteristic of modern times promote weight gain. The average person in North American gains nearly 9 kg between the ages of 25 and 55 yrs, and surprisingly this increase is caused by a minor imbalance (0.3% of calories yearly) between the energy intake and expenditure. Of the three components that comprise energy expenditure, resting metabolic rate has the greatest impact, as low basal energy expenditure correlates with weight gain. Energy expenditure normally increases after the ingestion of food, though in some individuals (e.g., those with insulin resistance) the thermic effect of food is lower than in

healthier more insulin sensitive subjects. The effect of physical activity on energy expenditure is greatly influenced by individual choice (**6**).

Body fuel mobilization from storage is required during fasting and exercise conditions (**Figure 2A**). This is accomplished by a fine tuned neuro-hormonal regulatory system involving the sympathetic nervous system and pancreatic insulin and glucagon secretion, in concert with circulatory levels of catecholamines, growth hormone and glucocorticoids. The contribution of these stimuli to body fuel mobilization and storage varies significantly depending upon the extent and intensity of the fasting period and of the exercise. Under basal circumstances insulin is secreted at a fixed rate, which keeps hepatic and muscle glycogen and fat stores steady with concomitant normoglycemia. In post-absorptive conditions, this steady-state is maintained primarily by a perfect balance between the release of pancreatic basal insulin and glucagon hormones into the portal vein, and endogenous glucose production, primarily derived from glycogen degradation and gluconeogenesis in the liver with a minor contribution by renal gluconeogenesis (**7**) is kept constant and meets the basal energy requirements of the brain and nerve tissues.

There is an obligatory demand for glucose by nerve cells for complete oxidation, thus glucose uptake and utilization is insulin-independent and proportional to the glucose concentration in the incoming arterial blood flow. Simultaneously, the presence of basal insulin levels together with elevated growth hormone and glucocorticoids in the peripheral circulation enables triglyceride hydrolysis in adipose tissue (lipolysis), which releases free fatty acids in sufficient quantity to provide other body tissues and organs, particularly the skeletal muscle, with their basal energy demand during an overnight fast. A comparable fuel mobilization process is also in place for periods of physical activity whereby there is often an exaggerated lipolytic rate with intense skeletal muscle fatty acid utilization, essentially regulated by basal plasma insulin in conjunction with elevated circulating catecholamines.

In the postprandial period, following oral intake, nutrients are digested and absorbed in the intestines, and there is predominantly fuel storage accompanied by less fuel mobilization (**Figure 2B**). The neuro-endocrine responses that surround the meal consumption are well described, and the ones that have received most attention recently are the "gut hormones". Specifically, the incretin effect of the glucagon-like peptide-one (GLP-1) and gastrointestinal inhibitory [insulin] peptide (GIP) has been recently recognized. These gut hormones are directly involved in augmenting pancreatic insulin secretion (GLP-1 and GIP, "incretin effect"), and in suppressing glucagon secretion. They also promote slowing of gastric emptying and induce anorexia via yet unknown CNS mechanisms (GLP-1 only). Stimulated pancreatic insulin secretion and glucagon suppression are responsible for the near complete inhibition of endogenous glucose production. The shift to high insulin-low glucagon balance in the portal system promotes hepatic glycogen storage, the formation of lipid particles and protein synthesis. In face of the transient postprandial hyperglycemia, elevated plasma lipids and high amino acid levels in the circulation, insulin enhances peripheral glucose and amino acid uptake with subsequent skeletal muscle glycogen and protein synthesis. In a net reversal of the fuel mobilization process, peripheral hyperinsulinemia also promotes free fatty acid uptake, triglyceride synthesis and storage in adipose tissue. This postprandial fuel storage period is interrupted by the next meal, and the fasting-feeding cycle restarts.

Insulin Resistance

The presence of insulin resistance characterizes type 2 diabetes mellitus and obesity and comprises several defects in insulin action at the skeletal muscle, adipose tissue and at the liver. Earlier on, in the development process of type 2 diabetes there is a decrease in insulin–mediated glucose metabolism in skeletal muscle that contrasts with the augmented adipose tissue lipolysis. As a result, circulating levels of glucose and free fatty acids are elevated triggering additional pancreatic insulin release which leads to a state of compensatory hyperinsulinemia. These abnormal hormonal circumstances predispose subjects to further worsening of insulin resistance compounded by many years of "overeating" and "sedentary lifestyle". Most of the excess calories consumed over time will eventually be stored as fat depots in body areas other than the adipose tissue, referred to as "ectopic fat". Of particular interest are the abnormal fat deposits in the liver (fatty liver), in pancreatic islet cells and in skeletal muscle cell, the so-called "intra-myocellular fat". Moreover, in these ectopic fat cells, hyperinsulinemia promotes the formation and release of pro-inflammatory cytokines by preferentially stimulating the insulin-response elements of the mitogen-activated protein kinase (MAP-kinase) signaling pathway, which is discussed in more details below. Sustained hyperglycemia (glucotoxicity), intra-islet fat accumulation (lipotoxicity) and the presence of these pro-inflammatory cytokines lead to pancreatic beta-cell failure and favor the development of type 2 diabetes. The initial defect in this pathophysiological sequence is the decreased insulin-mediated glucose metabolism, which was originally described by DeFronzo RA et al. several years ago (**8**). Using the gold-standard "insulin clamp" procedure in combination with isotope dilution technique in order to assess the degree of insulin resistance, he was able to conclusively demonstrate impaired insulin-mediated glucose uptake, storage and oxidation both in normal

weight diabetic patients and in obese non-diabetic subjects. Both the fraction of glucose stored as glycogen and that partially (to lactate) or completely oxidized was equally decreased. These data raised the possibility for the first time that these hormonal and metabolic abnormalities occurred early in diabetes and were actually independent of the presence of obesity. In other words, these were possibly inherited in the genes and only made worse by environmental effect of excess fat accumulation. A series of subsequent elegant studies confirmed these findings and provided further insight into potential mechanisms to explain the insulin resistance.

The molecular pathways underlying the impairment in glucose uptake stimulated via insulin signaling in skeletal muscle and adipose tissue (**Figure 3**) were recently defined (**9**). The initial steps involve insulin binding to its receptor that spans the cell membrane, causing auto-phosphorylation of the insulin receptor at "tyrosine residues" located in the intracellular segment of the trans-membrane protein molecule. The phosphorylated insulin receptor is then activated and acts as a kinase enzyme to stimulate the phosphorylation of 2 insulin signaling molecules in the cytoplasm, insulin responsive substrate, IRS-1 and IRS-2. The activation again occurs on "tyrosine residues" contained within the molecules of IRS-1 and IRS-2. Subsequently, the activated IRS-1 and IRS-2 stimulate the production of phosphoinositol-3-kinase (PI-3-kinase), which in turn stimulates movement of intracellular vesicles containing the glucose transporter protein, GLUT4, from the cytoplasm to the cell surface. GLUT4 then facilitates the transport of glucose molecules into skeletal muscle and adipocytes, cells that express GLUT4. Therefore, insulin binding to its surface receptor results in an increase in glucose uptake from extracellular fluid (*in vivo*, from plasma) into these insulin-sensitive cells and the intracellular glucose molecules are then directed towards either storage as glycogen or oxidative pathways. A reduced effect of insulin to stimulate glucose uptake ("insulin resistance" in muscle and fat) might result from one or more defects at any point along this signaling cascade and this has not yet been determined.

Additional studies (**10,11**) further characterized the role of fatty acids in the impaired activation of the proximal insulin signaling molecules in muscle. The increased accumulation of fatty acids and derivatives in the cytoplasm, presumably derived from continuous tissue delivery due to chronically elevated plasma free fatty acids (FFA) suggested there was a direct link between this and the molecular defects responsible for insulin resistance. Following the demonstration in skeletal muscle that intracellular fatty acid metabolites, such as fatty acyl-CoA, diacylglycerol, and ceramides shifted the phosphorylation site(s) of insulin signaling intermediate molecules from "tyrosine residues" (activation pathway) to "serine/threonine residues" (inactive pathway) a causative relationship between the accumulation of intracellular fat metabolites and insulin resistance was proposed. The phosphorylation of "serine/threonine residues", as opposed to "tyrosine residues" on the insulin receptor substrates IRS-1 and IRS-2 was shown later to be mediated by the formation of protein kinase C (PKC). The enhanced formation of inactive signaling molecules was accompanied by a subsequent reduction in the trans-membrane glucose transport and metabolism. More recent observations (**12,13**) have indicated that, in addition to the increase in fatty acid supply, there is also a significant decrease in mitochondrial fat oxidation in skeletal muscle cells in diabetic patients. This might explain in part why some individuals handle high fatty acid loads more efficiently than others. As we became aware of this new potential defect, many drugs capable of stimulating mitochondrial fat oxidation have been developed and are today widely used as insulin sensitizers, i.e., the PPAR gamma agonists, omega-3 fatty acids and thiazolidenediones.

There is an alternative pathway in the insulin signaling cascade, the mitogen-activated protein kinase (MAP-kinase), which is responsible for stimulating cell proliferation, migration and inflammation. The proliferative MAP-kinase and the metabolic (PI-3 kinase) pathways are activated simultaneously following insulin binding to the membrane receptor. The activation of the MAP-kinase is of importance to the extent that, unlike the metabolic pathway, it is not blocked by the intracellular accumulation of fatty acid derivatives (**14**) and, in view of the compensatory hyperinsulinemia, tends to show an exaggerated response with local release of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor alpha. There is evidence that the state of metabolic insulin resistance worsens in the presence of these inflammatory biomarkers and a vicious cycle is created (**12**). Thus, in terms of molecular physiology, peripheral insulin resistance is characterized by the following main abnormalities: i) a genetically yet unidentified inherited proximal defect in insulin signal transduction; ii) an increased supply of fatty acids and decreased fat mitochondrial oxidation, with subsequent intra-cellular accumulation of acylated fatty acid derivates; and iii) increased release of local pro-inflammatory cytokines favored by hyperinsulinemia. This information becomes of considerable significance as it enables the development of novel strategies designed to effectively prevent and delay the progression from pre-diabetes to diabetes and provides opportunities for new treatments for patients with type 2 diabetes, all based on modifications of harmful environmental factors.

Diabetes Prevention Strategies

The cornerstone of diabetes prevention and treatment is the management of several nutrient-related abnormalities which lead to excess body weight, more specifically excess body fat and body fat redistribution. There is a general agreement that in those individuals genetically predisposed to develop diabetes, i.e. first degree relatives of patients with known type 2 diabetes, an aggressive plan must be outlined to avoid the progression of insulin resistance and failure of beta-cell pancreatic insulin secretion. These include nutrient manipulations and encouraging physical activity. Also, there are new pharmacological agents that have been shown to help in reducing and maintaining weight loss and re-directing nutrient absorption and metabolism in patients with diabetes. Bariatric surgery has also gained *momentum* and is a valid and beneficial alternative, though limited to extreme conditions of morbid obesity. Novel promising gastrointestinal surgical procedures, referred to as "metabolic surgery" are currently under development and investigation, which go beyond reduction of excess body fat and may actually address the more complex nutritional-hormonal derangements typically seen in obese individuals.

Principles of Dietary Manipulations **-**

This is an extensive topic with numerous citations in the literature and the "internet", and because of space limitations we will discuss solely the principles that guide most dietary recommendations and guidelines, based exclusively on solid scientific data.

There is no question that in order to achieve body weight loss a low-calorie diet is necessary. This principle is incorporated in pretty much all diets designed to induce weight reduction. There may be issues regarding whether these low calorie diets should be predominantly low in carbohydrates or low in fat content, or both. The American Diabetes Association (**15**) and the Mayo Clinic (**16**) propose a reduction in both sources of calories further emphasizing the fact that any changes in dietary habits must be individualized. To be effective, these changes should respect personal preferences and cultural factors. In individuals with hypertriglyceridemia, low carbohydrate intake should be preferred, since this might impact on the effort to reach the goals set for plasma triglyceride levels. Although, theoretically less fat intake provides greater weight loss than less carbohydrate intake per unit mass, a proportionate reduction in both fat and carbohydrate content in the consumed food tends to be more efficacious and long-lasting in subjects who are dieting to lose weight.

Several high protein diets (**17,18**) have been proposed with different combinations, such as the Atkins (high protein, high fat) and the South Beach (high protein, low fat). When scientifically tested however in long-term randomized clinical trials these dietary regimens are not much different from one another or from any other tested low calorie diet program (**19**). The data indicate that there is an initial loss of body weight, but this eventually dissipates and the body weight returns to baseline on the average after 1-2 years. Also, there is a noticeable poor long-term adherence to these high protein diets and it should be used with caution in individuals with renal dysfunction.

The notion of glycemic index is somewhat artificial since these are derived from the intake of single food products, one at a time, when in fact most people consume mixed meals. However, the emphasis on the preferential use of food products with nutrients that have low glycemic index has been shown be beneficial and of some clinical significance (**20**). Essentially, when people consume meals with low glycemic index nutrients the postprandial hyperglycemia is attenuated and this softens the demands on a failing pancreas. As a result, individuals prone to develop type 2 diabetes tend to prolong the functional reserve of the pancreatic beta-cells and delay the clinical manifestation of beta-cell exhaustion and insulin deficiency. This was elegantly demonstrated in the recently completed NIH sponsored Diabetes Prevention Trial (**21**).
It is generally recommended that persons susceptible to diabetes consume complex, as opposed to simple carbohydrates and that these be combined with products containing other nutrients, particularly proteins and high soluble fibers. It is noteworthy that in a recent nationwide survey in the United States, sugar-added drinks were found to be responsible for nearly one-half of the daily caloric intake of overweight children and adolescents (**22**). As a consequence, government agencies supported by the food industry are interested in improving the nutritional profile and halting the growing epidemic of obesity in youth, by implementing new legislation and incentives to make unsweetened low-calorie drinks affordable in the market, mandate that public schools offer healthier food products, and put more emphasis on education about nutrient selection, dietary habits and lifestyle choices (**23**).
The Mediterranean diets are very popular and have been embraced by most health care providers that promote low calorie diets containing a low-saturated and high-unsaturated fat ratio. In combination with other Mediterranean habits, these diets have been associated with important cardiovascular and metabolic benefits (**24**). Diets rich in omega-3 (some fish) fatty acids are also very popular and represent an option with proven efficacy in the prevention of metabolic and cardiovascular disease, even though a higher mortality due to hemorrhagic stroke in Eskimos and in those residing in the North Pacific area of the United States, where fish consumption is overwhelming has been reported (**25**).
At the Texas Diabetes Institute, University of Texas at San Antonio we promote the principles incorporated into the

DASH diet (Dietary Approaches to Stop Hypertension), first introduced by the Nephrology Society (**26**). The DASH and similar diets have been associated with a delay in the development of type 2 diabetes and slowing the progression of atherosclerotic cardiovascular disease in several longitudinal clinical studies (**27-30**). The DASH diet recommends the use of low salt and a low calorie intake, giving preference to natural nutrients such as low-fat milk products over meat products and a diet rich in vegetables, fruits and nuts. In addition to its efficacy this diet has an exceptional adherence rate, which is easier to sustain for life. The cost of the nutrient components nonetheless is high and this is probably the main downside that hampers full compliance with the DASH diet.

Physical Activity and Exercise -

There is no question that acute exercise, training and regular physical activity is associated with improvements in insulin sensitivity and reduced cardiovascular risk. In order to further validate the observations that physical activity can effectively reduce the progression towards type 2 diabetes, a few seminal studies have uncovered the potential mechanisms by which exercise promotes more efficient insulin action in peripheral tissues. These recently published studies have convincingly demonstrated that acute exercise induces the synthesis and storage of neutral fat (triglycerides) surrounding, not inside, skeletal muscle fibers (**31**) and restores mitochondrial number and function (**32**). These changes typically found in marathon runners and in other endurance athletes are accompanied by increased insulin sensitivity and tend to minimize fatty-acid induced insulin resistance, thus facilitating glucose control in diabetic patients.

Pharmacological Therapy -

Most overweight/obese subjects with type 2 diabetes require pharmacological therapy at some point during therapy to help with loss and maintenance of body weight. This is despite aggressive approach with comprehensive nutritional assessment, detailed dietary instructions, constructive feedback with reinforcement and strong recommendations for behavioral changes. Approximately 80-90% of patients with type 2 diabetic patients are eventually started on some sort of drug treatment with the few available agents capable of promoting satiety and reducing the appetite. In long-term clinical trials, the subcutaneous injection of the GLP-1 agonist and anti-diabetic drug exenatide, 10 mcg given twice daily before meals, has been shown to induce sustained 4.5 to 6 kilograms of body weight loss over a 3-year period (**33**). One other interesting pharmacological approach to reducing body weight by a decrease in calorie intake is the injection of a long acting preparation (exenatide LAR, 2.0 mg) administered once a week, though its use is limited to obese diabetic subjects. Using this once a week preparations, a significant 3.8 kilogram weight reduction over the short-period of 15 weeks was documented in obese diabetic patients (**34**). The use of combination injections of pramlintide and metreleptin is yet under clinical investigation and is expected to be approved soon for general use in the treatment of obesity. Data obtained so far in short trials of 20 weeks duration demonstrate an impressive 15% reduction in body weight (**35**). One additional GLP-1 agonist has been launched recently in the market (Victoza, 1.2-1.8 mg once a day) and various others are currently under investigation in the US market. These GLP-1 analogs promote satiety and curb the appetite by concomitantly slowing gastric emptying and affecting hypothalamic centers responsible for the regulation of food and calorie intake. Dietary restriction is necessary and it is easily accomplished in view of the lack of appetite and the fullness sensation created by the action of these agents. Most other drugs and pharmacological agents announced to promote weight lose are either inefficient, lack safety and/or have no scientific evidence to support the claims.

Body Fat Redistribution

The recent demonstration that there is a substantial amount of ectopic fat accumulated in tissues and organs other than the adipose tissue, which is actually responsible for most of the metabolic derangements leading to insulin resistance and diabetes, has generated interest in new therapies aimed at redistributing the fat depots from ectopic to eutopic areas. The disappearance of muscle ectopic fat, i.e., intra-myocellular triglycerides, has been clearly demonstrated in muscle biopsy specimens following substantial weight loss with either a low-calorie diet or bariatric surgery (**36**). Of greater interest, perhaps, the documentation of the decrease in intra-muscle fat depot was closely related to an improvement in insulin sensitivity. Moreover, using serial computerized tomography in a group of Hispanic diabetic subjects treated with the PPAR-gamma agonist pioglitazone for a period of 6 months, a decrease in visceral (ectopic) fat simultaneous with an increase in subcutaneous (eutopic) fat was convincingly demonstrated (**37**). These observations suggest that in order to slow the progression towards the development of type 2 diabetes a shift in body fat distribution from ectopic to eutopic areas may be of critical importance. In contrast however, no metabolic and cardiovascular benefits were shown in studies evaluating the effects of weight (fat) loss in 15 women who underwent liposuction with surgical removal of subcutaneous fat for esthetic purposes. Despite the noticeable decrease in the apron-type subcutaneous fat depot and a measurable reduction in the waist circumference, there was no significant change in fasting plasma glucose, insulin and LDL cholesterol levels 6 weeks after surgery, both in normal glucose tolerant and in type 2 diabetes (**38**). Therefore, insulin resistance and cardiovascular risks were not affected, again, reinforcing the notion that if an

improvement in insulin resistance is expected body weight and fat loss must be accompanied by depletion of ectopic fat deposited in tissues and cells. These findings indicate that by removing the excess intra-cellular fatty acid derivatives, insulin sensitivity improves, thus entirely in agreement with our current understanding of the molecular defects responsible for insulin resistance in skeletal muscle.

In summary, diabetes prevention and treatment requires aggressive implementation of strategies, including dietary manipulations, lifestyle modifications, increased physical activity and use of pharmacological therapy, aimed at body weight and fat reduction with maintenance, particularly in obese genetically predisposed individuals. All interventions should promote efficient redistribution of ectopic body fat, decrease the accumulation of intra-cellular acylated fat derivatives and improve tissue insulin sensitivity. These steps provide the basis for current rationale in programs designed to delay the appearance and progression of type diabetes. The development of type 2 diabetes requires the combination defects of insulin resistance and relative insulin deficiency, both of which are inter-related and genetically determined. The global epidemics of obesity and sedentary lifestyle have exposed the inherited genotypes of diabetes, and we have learned that it is the FAT "inside", not the one "outside", which matters when implementing nutrologic strategies to prevent and treat type 2 diabetes.

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Figure1 - Natural History of Type 2 Diabetes

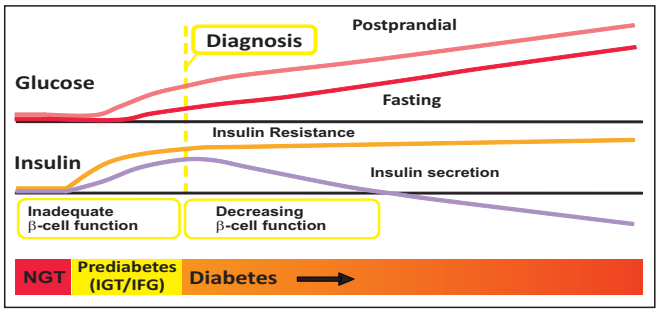

Figure 2A - Fuel Mobilization - Fasting and Exercise

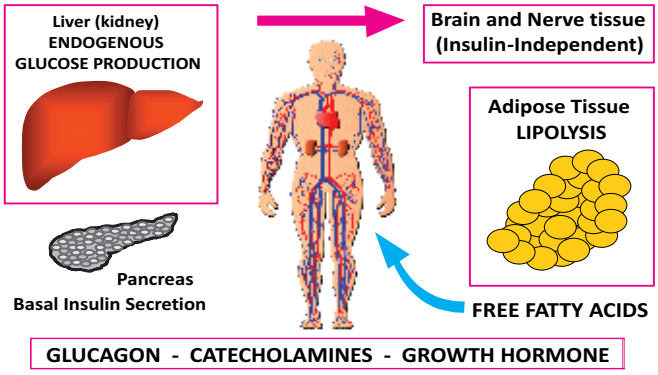

Figure 2B - Fuel Storage - Postprandial

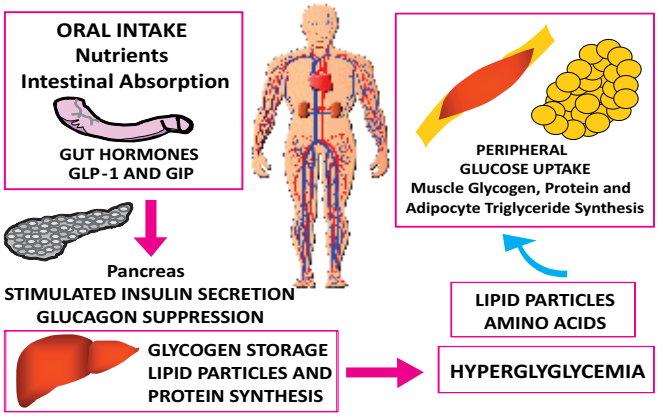

Figure 3 Insulin Resistance and Obesity: Effects of Free Fatty Acids on Muscle