Received: 4 June 2018 | Revised: 4 September 2018 | Accepted: 8 October 2018

DOI: 10.1111/pedi.12787

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REVIEWS AND COMMENTARIES

Does obesity cause type 2 diabetes mellitus (T2DM)? Or is it the opposite?

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Obesity is believed to be a promoter of type 2 diabetes mellitus (T2DM). Reports indicate that severe obesity in childhood and adolescence increases the risk of T2DM in youth and young adults. T2DM, which is commonly asymptomatic, frequently is not recognized until random blood glucose is measured. Screening blood glucose levels measured in obese individuals are more effective for identifying undiagnosed persons, than screening the general population and therefore introduces a selection bias for discovery. The following commentary will indicate why these observations do not indicate that obesity is the cause of T2DM. Also, it will be shown that the insulin resistance of T2DM occurs primarily in the muscles of lean individuals predisposed to diabetes before they become obese. This insulin resistance is not secondary to, but instead, is the cause of the excessive fat accumulation associated with T2DM. Moreover, this early muscle insulin resistance is the etiology of the hyperlipidemia and excess fat accumulation characteristic of T2DM.

KEYWORDS

diabetes, insulin resistance, obese non-diabetics, obesity

1 | INTRODUCTION

It is currently accepted that obesity is nearly a global epidemic.[1] The prevalence of childhood obesity in the United States is also rising in a parallel fashion.[2] Obesity is defined as an excessive amount of body fat. Overweight and obese individuals are defined by measures of weight and height that provide an index of one's mass, referred to as a body mass index (BMI). A BMI of 30 kg/M^2 or greater is the definition of obesity.[3] Public health publications indicate that the risks for type 2 diabetes mellitus (T2DM), heart disease, and high blood pressure are increased in individuals who are obese.[4] The relationship between obesity and diabetes was noted as early as 1916 by Elliot P. Joslin.[5] Since the 1950s, the conventional wisdom has been that a net positive energy balance causes obesity. When a person consumes more energy than needed for daily operation, the excess energy is stored primarily as fat, and a small amount is stored as glycogen. Simply put, one gets fat by eating too much of food. Another interesting observation made in the 1950s was that a 10% reduction in body weight could result in the disappearance of clinical diabetes mellitus in obese individuals with that diagnosis.[5] These observations support the current belief that obesity causes T2DM.[6] It has been noted that severe obesity in childhood increases the risk for T2DM in youth and early adulthood.[7] Another observation from the early 1990s by Kahn and Porte was that more than 80% of individuals diagnosed with T2DM are obese, but 85% of obese people never get diabetes.[8] Recent data from the National Diabetes Statistics Report (2017)[9] indicates that 87.5% of adults with diabetes are overweight/obese, but the 18.4 million people who are overweight/obese and have diabetes only represent 13.8% of the total overweight/obese adult (>18 years) population identified in the United States in 2016.[10] It is commonly believed today that overeating is the primary cause of obesity which in turn is a key cause of T2DM. Therefore, many people believe that "eating healthy (less calorie dense food) combined with exercise" will prevent T2DM. A large multicenter study, "The Diabetes Prevention Program" seems to support that concept.[11]

The Mechanism of Obesity: If one is interested in preventing obesity, it is useful to understand how it occurs. Humans (children and adults) consume protein, carbohydrate, fat, and non-nutritive fiber plus essential vitamins as part of the substrate required for normal growth and development as well as physical maintenance. When more nutrients are consumed than needed, the excess is stored primarily as energy in the form of fat and glycogen. The major form of stored energy in humans is fat (triglycerides), which accumulates primarily in

adipocytes that are located subcutaneously and around organs. which can be seen physically and described socially as overweight or obese depending on the degree of excess fat.

Protein is absorbed as amino acids, which provide the building blocks for muscle, collagenous infrastructure, and other protein components of the body. The amount of protein recommended for normal growth and development for all ages is 2.8 g per kilogram of body weight.[12] One should keep in mind that the amount of protein needed for periods of rapid growth, such as early childhood may be more than 3 g per kilogram of body weight, but with older age when maintenance only is required the number may drop to 1 g per kilogram body weight. When too much protein is eaten, it is converted to glucose for storage as fat, but the body must then excrete the extra nitrogen to avoid the decreased appetite, nausea, and headaches associated with elevated nitrogen.

Carbohydrate is absorbed from the gastrointestinal tract primarily as glucose and it is utilized directly by the brain, nervous system, red blood cells, heart, and other muscles as the primary energy source. Excess glucose can be stored in muscle, and the liver as glycogen. More commonly excess glucose is metabolized into fatty acids and glycerol-3-phosphate in adipocytes. These two substrates combine to produce triglycerides, the fat storage form, by the esterification of the fatty acids on to glycerol-3-phosphate. Glycerol-3-phosphate is required to provide the backbone for the production of triglycerides, and it is created inside the fat cells from glucose. Glucose requires the action of insulin for its intracellular transport before it is metabolized into glycerol-3-phosphate. Fatty acids are also transferred across cell membranes by a fatty acid transport protein into the cytoplasm of fat cells.[13] One fatty acid transporter (CD36/SR-B2) has been noted to be insulin induced.[13] Thus, intracellular fat production requires: glucose, fatty acids, and insulin.

Fats are ingested primarily as triglycerides, which are hydrolyzed by many lipase enzymes but particularly pancreatic lipase which releases fatty acids and monoglycerides into the gastrointestinal tract for absorption. These fat droplets are dispersed by the motility of the gut to produce micelles, which can attach to the surface of the enterocytes of the intestinal wall and absorbed. When absorbed, they are reassembled into triglycerides and packaged along with cholesterol and lipid soluble vitamins into chylomicrons. Chylomicrons then flow into the circulation through lymphatic vessels, which drain into the general circulation in the large veins in the thorax. These triglycerides are hydrolyzed and release fatty acids and monoglycerides. The fatty acids are transported with the help of insulin into muscle cells for functional energy and adipocytes for storage as fat. Fatty acids and glucose are the nutrients that are utilized by the body for the energy required to provide muscle function, with the excess being stored in fat cells for later use.

Fatty acids are utilized by all tissue containing mitochondria to provide energy. When energy is needed from the stored fat, fatty acids are then released by hydrolysis and transported to the tissue that needs the energy. The remaining glycerol, however, cannot be recycled into glycerol-3-phosphate because the enzyme, glycerol kinase, required for glycerol phosphorylation does not exist in adipocytes. Thus, new glycolytic intermediates must be formed from newly transported glucose across the cell wall a process that requires insulin. Both glucose and insulin are required for the production and storage of fat in adipose tissue and are essential to establish and maintain obesity. It has also been noted that as fat stores increase and the size of adipocytes increase the cells seem to be less responsive to the presence of insulin for glucose transport. A mechanistic explanation suggests that the physical change of the receptor configuration caused by stretching the cell surface of enlarged adipocytes reduces the efficiency of glucose transport. A biochemical explanation is that over-nutrition cause's oxidative stress, which results in oxidation-induced inactivation of the glucose transporter GLUT4.[14] Thus, individuals with excessive fat storage have been noted to have higher insulin levels and are said to have insulin resistance, which is described as the cause of T2DM. This form of insulin resistance is acquired in proportion to the amount of accumulated fat. Effective insulin action is essential for fat production and accumulation. Without insulin action, one cannot store body fat in spite of excessive nutrient availability as seen clinically during the evolution of type 1 diabetes. People with type 1 diabetes are noted to lose weight and fat while consuming excessive quantities of food as an early characteristic sign. If significant or important insulin resistance occurs in fat tissue, it is manifest as weight loss and reduction of total body fat. Pathologic insulin resistance involving fat tissue was reported in several subjects who developed insulin receptor antibodies which blocked the cellular action of insulin[15,16] on all insulin-requiring tissues of the body. Each of those individuals, lost weight in the form of subcutaneous fat with ketonuria while having circulating insulin levels greater than100 μU/mL. Thus, insulin resistance caused by obesity is physiological and acquired in parallel with increased fat mass. Eighty-seven percent of overweight/obese individuals do not develop diabetes but have this same degree of fat-induced insulin resistance; this suggests that the degree of insulin resistance associated with obesity and it is not sufficient to cause diabetes. A suggested estimator of human insulin sensitivity is the homeostasis model assessment (HOMA). It has some association with sensitivity in human subjects.[17] HOMA insulin resistance (HOMA-IR) in a type 2 diabetic group (BMI 41.8 kg/M^2) has been reported as 10.3 $\pm$ 7.7[18] while in an obese non-diabetic group with a somewhat greater BMI (BMI 46.5 kg/M^2) HOMA-IR was reported to be 5.8 $\pm$ 1.9.[19] The higher HOMA number in the diabetics with a lower BMI suggests greater insulin resistance in obese diabetics than is caused by the obesity.

1.1 | What is diabetes mellitus?

Diabetes mellitus is a condition of chronic hyperglycemia that causes physical damage, physiologic dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, blood vessels, and the brain. The specific glucose level definition of diabetes is an 8-hour post fasting blood glucose >126 mg/dL or a 2-hour postprandial blood glucose >200 mg/dL.[20] Two common forms of diabetes are type 1, which occurs when endogenous insulin production stops, and type 2 where insulin production continues but the tissue response to insulin is reduced. T2DM is commonly associated with overweight and obese individuals. Thus, the belief that obesity causes T2DM. The basic mechanism for obesity is excess glucose and insulin. When more glucose (energy) is available in the body than required for physiological, cardiac, and skeletal muscle function, it is stored in adipocytes as

triglycerides or "fat." The most common pathway is the ingestion of carbohydrates and proteins, which stimulate increased endogenous insulin release, allowing glucose utilization for muscle function and storage of unneeded glucose as fat. Without glucose and insulin, the body cannot make or store fat. The next pathway for excess fat accumulation is when elevated insulin levels occur in response to cardiac and skeletal muscle resistance to the action of insulin. Skeletal muscle is the largest tissue in the human body and plays a major role in locomotion and body metabolism. It is estimated to be responsible for 80% of insulin-stimulated glucose disposal.[21] Skeletal muscle insulin resistance compromises intracellular glucose and fatty acid transport, which reduces these essential fuels for skeletal and cardiac muscle function. This reduction in the substrate for energy production results in elevated glucagon to increase hepatic glucose production and available supply. The increased hepatic glucose production (not transported into muscle for energy in spite of elevated insulin) seems to stimulate fatty acid release in an attempt to provide an alternative substrate for muscle energy. The increased lipid levels do not reduce hepatic glucose production. This may occur because of α-cell insulin resistance, which blunts the normal suppression of glucagon release caused normally by insulin,[22] or because increased lipid levels do not increase mitochondrial adenosine triphosphate (ATP) production in muscles.[23] Thus, a new steady state of increased glucose and insulin production provides an abnormal metabolic environment ideal for fat production and storage in adipocytes. Magnetic resonance spectroscopy (MRS) in subjects with muscle insulin resistance has shown intramyocellular and liver "ectopic fat accumulation."[24] This abnormal metabolic environment can explain increased fat accumulation in the liver, which contains glycerol kinase and therefore does not require insulin for triglyceride production and results in a separate problem termed fatty liver disease.[25] The intramyocellular deposition of ectopic fat remains unexplained.[24] When intracellular glucose availability is compromised by insulin resistance in the myocardium, fatty acid metabolism for energy becomes more important for normal myocardial function. Fatty acids require free carnitine for transport into mitochondria to produce the required ATP. Carnitine is made endogenously by the liver and kidney and is eaten as a component of animal protein.[26] Carnitine, therefore, is generally available to provide sufficient fatty acids for myocardial and skeletal muscle function. However, when free carnitine is esterified by the excessive production of organic acids associated with diabetes this compound is not reabsorbed as well by the renal tubules and is lost in the urine. This "urinary leak" causes increased loss of carnitine in the urine,[27] resulting in reduced free carnitine and a compromise in fatty acid availability as an alternative substrate for energy metabolism in the heart. This may explain the observed impaired mitochondrial activity found in patients with T2DM.[23] Thus, muscle insulin resistant diabetes causes a compromise in energy availability from both elevated glucose and elevated fatty acids for muscle function. This apparently stimulates production of substrate needed for the ATP required to maintain normal heart and muscle function results by continuous gluconeogenesis and elevated insulin levels. This unending metabolic demand requires constant insulin production and release. This does not allow the normal interval for the production and storage of insulin, which occurs routinely during the hour following an ingested glucose bolus.[28] This stored insulin is then released as a bolus termed the first phase insulin response following food ingestion. This first phase insulin response is lost during the progression of patients to overt T2DM and constant hepatic glucose release caused by chronic hyperglucagonemia or hepatic insulin resistance. The constant insulin release without a rest interval for storage is characteristic of T2DM. The continuous infusion of glucose from the liver is in response to the continued release of glucagon which is not being normally suppressed by the elevated insulin levels. Obese individuals with impaired glucose tolerance (IGT) or overt T2DM have been noted to have both elevated insulin and glucagon levels in the fasting state,[26,27] while obese individuals without diabetes or IGT do not have elevated fasting glucagon levels.[29,30] With the passage of time, the islet cells capacity to make sufficient insulin to maintain normal glucose tolerance declines.[31]

It has been observed that US blacks, American Indians, Hispanics, and Pacific Islanders have a greater propensity for developing T2DM.[9] Several studies have found that members of the groups named above have high levels of insulin circulating before they become fat and that insulin resistance was found to be isolated in the muscle mass.[32] The individuals who have increased resistance to the action of insulin in their muscles always have higher circulating insulin levels than the standard patient in the fasting state. Skeletal muscle is the major site of glucose uptake in the postprandial state in humans. Under euglycemic hyperinsulinemic conditions, 80% of glucose uptake occurs in skeletal muscle.[33] Studies using the euglycemic hyperinsulinemic clamp and femoral artery/vein catheterization to quantitate glucose uptake have allowed investigators to quantify leg muscle glucose uptake. Because adipose tissue uses 5% of an infused glucose load and bone is metabolically inert, the great majority of leg glucose uptake is accounted for by skeletal muscle. During physiological hyperinsulinemia (80-100 U/mL), leg muscle glucose uptake increases linearly with time, reaching a plateau value of 10 mg/kg leg weight per minute after 60 minutes.[34,35] In contrast, lean pre-T2DM subjects, have a delay in the onset of insulin action and the ability of insulin to maximally stimulate glucose uptake is markedly blunted. During the last hour of an insulin clamp, insulin-stimulated leg muscle glucose uptake is reduced by 50% in subjects with T2DM.[35] These studies support the notion that the primary defect in insulin action in patients with T2DM resides in the skeletal muscle and this precedes the clinical diagnosis of diabetes.

Multiple investigators have unequivocally demonstrated that lean, normal glucose tolerant (NGT) offspring of two parents with T2DM exhibit moderate to severe skeletal muscle insulin resistance.[36] As genetically predisposed (muscle insulin resistant) individuals progress from NGT to impaired glucose tolerant (IGT), insulin sensitivity declines in response to increased fat accumulation but glucose tolerance deteriorates minimally, likely because of a marked increase in insulin secretion. Similar observations have been made in Pima Indians[35] and Mexican Americans[37] and Caucasians residing in San Antonio.[31] These results, spanning a wide range of ethnic groups, clearly demonstrate that insulin resistance, and not insulin deficiency, initiates the sequence of events leading to the development of T2DM. However, progressive β-cell failure to respond to glucose stimulus is required and ultimately is essential to T2DM becoming fully manifest.[30] This β-cell functional failure has been attributed to the decline

of the "incretin effect."[38] The incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are responsible for the amplification of insulin secretion when glucose is taken in orally as opposed to intravenously. GLP-1 is secreted from L cells in the intestinal ileum. GLP-1 increases glucose transporter 2 expression in pancreatic β-cells[38] which increases β-cell sensitivity to glucose for increased insulin secretion, while also restricting glucagon release from the α-cells[39] and reducing hepatic glucose production. The first step of β-cell failure and IGT occurs when postprandial GLP-1 levels begin to decline.[39] Prospective studies in human and non-human primates have conclusively demonstrated that insulin resistance and hyperinsulinemia precede the development of IGT and that IGT represents the forerunner of T2DM. Studies in NGT first-degree relatives of diabetic individuals and in the offspring of two diabetic parents indicate that the inherited defect in insulin action results from an abnormality in the glycogen synthetic pathway in muscle and more proximal defects in glucose transport, phosphorylation, and insulin signal transduction.[40] As the insulin resistance progresses, muscle glucose uptake becomes further impaired, and the postprandial rise in plasma glucose concentration becomes excessive together with exaggerated insulin output. This increase in basal hyperinsulinemia is sufficient to maintain the fasting plasma glucose concentration within the normal range. Nonetheless, there is an excessive postprandial rise in plasma glucose concentration, and a longer time is required to restore normoglycemia after each meal. This is explained by the loss of first phase insulin response and the failure of postprandial glucagon suppression, which is explained by insulin resistance in the muscle and the pancreatic α-cells of the islets of Langerhans.[22]

An apparent second step in the progression toward T2DM is the reduction in the production of the incretin IGF-1 from the small intestine. The function of IGF-1 is to enhance insulin release from the β-cells in response to glucose and the blunting of glucagon release, which normally reduces glucose release from the liver. It has been reported[35] that declining postprandial IGF-1 parallels impairment in glucose tolerance. This reduced insulin production, I plus increased hepatic glucose production, results in higher postprandial glucose levels.[41] Eventually, the compensatory hyperinsulinemia declines and is no longer sufficient to maintain the fasting glucose concentration at the basal level. The development of hyperglycemia in association with the failing glucose stimulated β-cell secretion of insulin results in the clinical diagnosis of diabetes and the addition of supplemental exogenous insulin to achieve normal blood glucose levels. This results in increased fat accumulation.

The appropriate biologic response for individuals who have inborn muscle insulin resistance is to have elevated insulin, glucose and fatty acid levels to ensure that the heart and skeletal muscle have sufficient energy substrate available to sustain normal cardiac and muscle activity. Thus, individuals who have T2DM are genetically predisposed to muscle insulin resistance, and therefore, to become overweight or obese. Currently, there is no apparent link between the predictive hyperinsulinism in NGT prediabetic subjects and low GLP-1 levels, which is first noted as IGT occurs.[42] Whether there is a genetic link or the loss of IGF-1 production is an acquired component of T2DM is currently unknown.

1.2 | Conclusion

Obesity is associated with an increased risk of developing T2DM. Excessive consumption of carbohydrate may result in earlier onset of T2DM in genetically predisposed individuals, but obesity is not the primary cause of T2DM. People who are genetically predisposed to develop T2DM are at high risk for becoming obese because of the inherent insulin resistance of their muscle and islet α-cells, which promotes increased glucose and insulin release. This resistance results in increased hepatic glucose production and elevated insulin levels which are the cause of obesity.

The natural result of increased glucose and insulin availability is increased fat production and storage, the hallmark of T2DM. Lean normal glucose tolerant individuals predisposed to develop T2DM can be identified before clinical diabetes by measuring elevated fasting insulin and glucagon levels.[29] The most direct prevention of T2DM would be correcting the innate muscle insulin resistance that causes this abnormal endocrine and metabolic milieu. The resulting lower insulin levels and reduction of excessive hepatic glucose production would reduce fat accumulation and β-cell failure. Currently, that intervention is not available.

Agents (metformin, and GLP-1 receptor agonists), which reduce hepatic glucose productions in individuals with T2DM do cause some weight loss and fat reduction. Metformin has not prevented T2DM,[11] and GLP-1 receptor agonists have not been tested as a preventive agent. Since neither of these agents corrects the basic problem, they are unlikely to be the solution. Thiazolidiediones (TZDs) are compounds that increase insulin-mediated peripheral glucose disposal (insulin sensitivity), which occurs predominantly in skeletal muscle.[43] TZDs have been shown to prevent T2DM in patients with impaired glucose tolerance.[44] During a 3-year study the TZD-treated individuals continued to gain weight while having normalization of their HbA1c, free fatty acid and fasting c-peptide levels. The control group with impaired glucose tolerance in the present study also gained weight but their HbA1cs increased as well as their fasting c-peptide levels and 27% developed diabetes. Concerns about liver and heart toxicity have limited TZD use. TZD-treated patients have shown a reduction of muscle insulin resistance as manifest by reduced fasting c-peptide levels accompanied with lower HbA1c, fatty acid, and cholesterol levels.[42] These observations support the idea that correction of muscle insulin resistance will prevent T2DM.

The genetic metabolic features of individuals who have the propensity to develop T2DM result in the metabolic milieu required for the excessive production and storage of fat. Obesity by itself does not produce the metabolic and/or endocrine abnormalities found in individuals with T2DM. Obesity does not cause T2DM, but the evolution of T2DM does cause obesity.

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How to cite this article: Malone JI, Hansen BC. Does obesity cause type 2 diabetes mellitus (T2DM)? Or is it the opposite? *Pediatr Diabetes*. 2019;20:5–9. https://doi.org/10.1111/pedi.12787