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CHAPTER 1

Pathophysiology of Insulin Resistance and Type 2 Diabetes

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Type 2 diabetes (T2DM) is a recent addition to the medical conditions encountered in the pediatric age group. Prior to the 1980s, this condition was considered an "adult onset" disease and was rarely if at all diagnosed in childhood.[1] In the mid-1990s, first descriptions of T2DM in adolescents appeared and in parallel with the rising prevalence of obesity, this disease is now encountered more commonly in the pediatric age group.[2] The strong coincidental association with obesity stems from one of the key factors driving the development of T2DM—insulin resistance.[3] To develop T2DM, two defects must be present: insulin resistance and β-cell failure. Importantly, insulin resistance is a common trait in the general population as well as in obese children and adolescents.[4] Most insulin resistant individuals do not develop diabetes because their β-cells are able to compensate appropriately for the ambient resistance by secreting more insulin. Only failure to compensate appropriately (β-cell failure) will result initially in altered glucose metabolism (a group of conditions called "prediabetes") and may eventually progress to overt T2DM.

PATHOPHYSIOLOGY OF INSULIN RESISTANCE

Insulin resistance is a term used to describe a relative reduction in the metabolic response to insulin within its target tissues that are involved in glucose metabolism. These target tissues include the liver (hepatic glucose production is crucial for the fasting state), muscle (skeletal muscle glucose uptake governs the postabsorptive state), the endocrine pancreas, and adipose tissue. In the fasting state, normoglycemia is maintained by production of glucose by the liver via glycogen breakdown and gluconeogenesis. Hepatic glucose production is regulated by two main mechanisms: hormones secreted by the endocrine pancreas (glucagon and insulin) and by autonomic innervation.[5] The dominant hormone of the fasting state is glucagon that induces glycogenolysis and gluconeogenesis, as does the autonomic sympathetic arm.[6] Adipose tissue during fasting predominantly secretes free fatty acids (FFAs) produced via lipolysis to provide an alternative fuel to glucose while muscle takes up minimal glucose from the circulation. In the postabsorptive state dominated by insulin, hepatic glucose production is suppressed by insulin and the parasympathetic autonomic system while skeletal muscle glucose uptake is increased via trafficking of the glucose transporter 4 (GLUT-4) to the myocyte membrane. Adipose tissue in the postabsorptive state is characterized by enhanced lipogenesis. Importantly, the brain plays a dominant role in glucose metabolism via a mechanism called glucose effectiveness, which describes the effects of ambient glucose on its own uptake, independent of insulin.[7] Glucose effectiveness has a major impact on whole body glucose disposal in postabsorptive conditions (basal insulin concentrations) estimated at ~70%, while during exposure to typical postprandial insulin concentrations during a hyperinsulinemic-euglycemic clamp, the relative contribution of effectiveness to glucose disposal drops to ~30%. Following oral ingestion of a glucose load resulting in dynamic insulin concentrations, the relative effect of glucose effectiveness on whole body glucose disposal is estimated at 50%.[7]

All organs described above may demonstrate resistance to the effects of insulin to a certain degree. This resistance describes an inhibition of the signal transduction pathway that is involved in glucose metabolism (such as gluconeogenesis or glycogen metabolism) but not necessarily in other targets of insulin signal transduction such as lipid metabolism. Several mechanisms have been proposed to explain how this inhibition

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occurs. The leading theory is that fatty acid derivates of intracellular lipid droplets inhibit critical elements of the insulin signal transduction pathway.[8] These derivates (mainly fatty acyl CoAs and ceramide) inhibit insulin signal transduction via activation of activation of a serine/threonine kinase cascade (possibly initiated by protein kinase Cθ), eventually leading to phosphorylation of serine/threonine sites on insulin receptor substrate 1 and 2. Serine-phosphorylated forms of IRS 1 and 2 fail to activate PI 3-kinase resulting in reduced activation of glucose transport in skeletal muscle or suppression of gluconeogenesis in the liver.[9]

It is well established that in the pediatric age group, obesity is the leading feature associated with reduced insulin sensitivity.[10] Importantly, not all obese children are insulin resistant.[11] Recent studies performed in obese children and adolescents have shown that the pattern of lipid partitioning and not the degree of obesity per se is the best correlate of insulin resistance.[12] Lipid partitioning describes a specific profile of lipid depot distribution characterized by the deposition of fat within the intraabdominal compartment (visceral fat) as well as within the liver and skeletal muscle. The ability of subcutaneous fat to store excess lipid is probably the determining factor in the development of insulin resistance.[13] Those able to store large amounts of fat in this depot and spare liver and muscle maintain relative insulin sensitivity while those that are unable to expand it tend to accumulate excess intraabdominal and liver/muscle fat. It has been shown that, in equally obese adolescents (by means of body mass index and percent body fat) who differ in their degree of insulin sensitivity, those who are more resistant are characterized by larger amounts of visceral, intrahepatic, and intramyocellular lipid.[14] This can be expressed in other terms as the ratio of visceral fat to total abdominal fat—where those with a larger ratio (who are not necessarily more obese) tend to be much more insulin resistant and have greater amounts of intrahepatic fat. Similar to muscle and liver, lipid deposition within the pancreas has been shown to associate with altered β-cell function,[15] yet whether it has a direct role in the pathophysiology of T2DM is controversial.[16] Moreover, lower suppression of c-peptide secretion has been demonstrated in obese insulin resistant adolescents during euglycemic-hyperinsulinemic clamps along with reduced suppression of glucagon.[17] Whether "islet insulin resistance" and α-cell upregulation are a result of intrapancreatic lipid deposition is still to be determined. The mechanism of glucose effectiveness governed by specific central nervous system nuclei has also been shown to be altered in obese children with greater waist circumference (a surrogate of intraabdominal lipid deposition) and thus is unable to compensate for the reduction of insulin-dependent glucose disposal typical of whole body insulin resistance.[18]

A third important contributor to the typical insulin resistant milieu observed in obese children is adipose tissue that also may manifest resistance to the effects of insulin. As insulin suppresses lipolysis and induces lipogenesis in adipose tissue, resistance to its effects results in a shift of this balance toward greater lipolysis resulting in enhanced secretion of free fatty acids to the circulation.[19] Obese insulin resistant adolescents showed reduced suppression of FFA secretion during oral glucose tolerance tests and increased concentrations of fasting FFAs.[20] In obese children with normal glucose tolerance, an increase in adipose tissue insulin resistance was related to an increase in 2-h glucose levels. A tight relationship exists between visceral fat as well as the visceral-to-subcutaneous fat ratio with the adipose tissue insulin resistance. It has been shown that acute exposure to FFAs during euglycemic-hyperinsulinemic clamps results in an acute reduction of whole body insulin sensitivity.[21] Thus, basal and postprandial exposure to greater concentrations of FFAs, as shown in obese insulin resistant children, may have a similar peripheral effect enhancing overall resistance to the effects of insulin on skeletal muscle.

An additional mechanism driving the development of resistance to the effects of insulin in liver, muscle, and adipose tissue is the presence of inflammatory mediators. Subcutaneous and visceral fat is typically infiltrated by cells of the immune system, mainly macrophages, which secrete typical chemokines and induce the typical low-grade inflammatory profile that is commonly observed in obese adolescents.[22] The innate immune cell sensor leucine-rich pyrin domain containing 3 (NLRP3) inflammosome is one of the factors implicated in adipose tissue inflammation and the pathogenesis of insulin resistance. Obese adolescents with a high visceral-to-subcutaneous fat ratio show greater infiltration of macrophages within the subcutaneous fat depot and higher expression of the NLRP3 inflammosome-related genes. The increase in these markers of inflammation is present in parallel with a decrease in the expression of genes related to insulin sensitivity and lipogenesis. In addition, the concentration of ceramide within subcutaneous fat correlates with the expression of multiple inflammosome-related genes.[23] The presence of subcutaneous fat depot infiltration by macrophages and other cells of the immune system and upregulation of the NLRP3 inflammosome along with increased systemic and

intraadipose concentrations of ceramide may contribute to the limited expansion capability of subcutaneous abdominal adipose tissue leading to development of altered abdominal lipid partitioning and insulin resistance. In addition, macrophage infiltration into white adipose tissue induces increased lipolysis that further increases hepatic de novo triglyceride synthesis and hyperlipidemia due to increased fatty acid esterification.[9] Macrophage-induced adipose tissue lipolysis further stimulates hepatic gluconeogenesis, thus promoting hyperglycemia in both absorptive and postabsorptive states via increased fatty acid fluxes to the liver leading to increased hepatic acetyl-CoA that activates pyruvate carboxylase and thus induces increased glycerol conversion to glucose.[24] Thus, impaired insulin signaling in adipose tissue, caused by macrophage and other immune cell-induced inflammation, leads to a specific adverse substrate flux to the liver that results in accelerated intrahepatic lipid synthesis and thus to insulin resistance in the signal transduction pathway segment involved in suppression of gluconeogenesis.

Thus, insulin resistance in obese children is tightly linked to a typical lipid-partitioning pattern characterized by increased amounts of lipid within the main insulin-responsive tissues (skeletal muscle and liver) and a relatively reduced capacity to increase subcutaneous fat stores. Insulin resistance in the setting of childhood obesity thus results from a combination of altered functions of insulin-responsive target cells and the accumulation of macrophages that secrete proinflammatory mediators. Moreover, the adipose tissue of obese adolescents may also manifest insulin resistance resulting in lower suppression of lipolysis resulting in increased free fatty acid fluxes.

An additional factor affecting insulin sensitivity is the sex hormone profile. The landmark paper by Goran et al. described the transient yet substantial reduction (of ~33%) of whole body insulin sensitivity in midpuberty compared to prepuberty.[25] Of note, midpuberty is associated with a substantial reduction in insulin sensitivity similar to that observed during late pregnancy.[26] The mechanism underlying this phenomenon is probably that midpubertal insulin resistance is aimed at inducing a transient hyperinsulinemic state. The resistance to insulin in midpuberty is restricted to peripheral (skeletal muscle) glucose metabolism and the resultant compensatory hyperinsulinemia (the result of increased insulin secretion during that period[27]) may serve to amplify the anabolic effects of insulin on amino acid metabolism that are crucial during the growth spurt.[28] In obese adolescents, the nadir in insulin sensitivity in midpuberty recovers at the completion of pubertal development. Some argue that in the obese midpubertal adolescents, the reduction in insulin sensitivity does not completely resolve.[29] Thus, puberty represents an additional metabolic burden in adolescents who were obese and insulin resistant to some degree in prepuberty and sets the stage for the emergence of metabolic derangements such as T2DM and worsening of cardiovascular risk factors.[30] On the other hand, many obese adolescents manifest prediabetes and an altered lipid profile in midpuberty that may partially or completely resolve once pubertal development is completed.[31] One can argue that if altered glucose metabolism is evident in midpuberty, even if completely resolved at completion of pubertal development. This is a strong indication that the threshold of insulin resistance in which the obese adolescent cannot appropriately compensate by increasing insulin secretion has been reached. Thus future similar reductions in insulin sensitivity (such as pregnancy, acute illness, corticosteroid treatment, etc.) may manifest as hyperglycemia.

It is well established that obese children with impaired glucose tolerance manifest marked peripheral insulin resistance compared to those with normal glucose metabolism highlighting the crucial role of this factor in the development of diabetes.[32] These children also manifest the typical adverse pattern of lipid partitioning described above.[33] This along with normal pubertal hormonal changes and potential exogenous factors that may reduce insulin sensitivity may result in altered glucose metabolism and unraveling defects in insulin secretion.

PATHOPHYSIOLOGY OF β-CELL FAILURE

As indicated above, the majority of obese children are insulin resistant to some extent yet only a fraction of them develop altered glucose metabolism. The β-cells of these children fail to compensate appropriately. Upon facing peripheral insulin resistance, there are two basic mechanisms that allow compensation: secreting more insulin or reducing its clearance from the circulation. It has been shown that lower insulin sensitivity in children with normal and impaired glucose tolerance is associated with reduced insulin clearance reaching a trough that probably cannot be further reduced.[34] At this point, increasing insulin secretion is the only other compensatory mechanism. As glucose tolerance represents a continuum, rising glucose levels, even within the "normal" range, are already associated with subtle defects in insulin secretion, independent of insulin resistance.[35] It has been shown that obese children with impaired glucose tolerance already manifest significant defects