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PEDIATRIC TYPE 2 DIABETES (PS ZEITLER, SECTION EDITOR)

# Metabolic Basis of Ethnic Differences in Diabetes Risk in Overweight and Obese Youth

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**Abstract** The global pandemic of childhood obesity has led to increased risk for prediabetes and type 2 diabetes mellitus (T2DM). Studies have shown decreased insulin sensitivity and/or secretion with increasing adiposity and consistently observed greater risk for T2DM in obese, non-Caucasian youth. In the current review we describe recent advances in understanding how obesity and metabolic status in children and adolescents confers various risk profiles for T2DM among Latinos, African Americans, Caucasians, Asians, and Native Americans. These possible determinants include ectopic fat distribution, adipose tissue inflammation and fibrosis, and elevated plasma levels of nonesterified free fatty acids. Future work should aim to elucidate the ethnic-specific pathophysiology of T2DM in order to develop and implement appropriate prevention and treatment strategies based on different ethnic profiles of diabetes risk.

**Keywords** Obesity · Youth · Insulin sensitivity · Acute insulin response · Disposition index · Insulin secretion · β-cell function · Prediabetes · Hemoglobin A1c · Impaired glucose tolerance · Type 2 diabetes mellitus · Minorities · Ethnicity · Ectopic fat · Subcutaneous abdominal adipose tissue · Visceral adipose tissue · Intramyocellular lipid · Liver fat · Nonalcoholic fatty liver disease · Pancreatic fat · Adipose tissue inflammation · Adipose tissue fibrosis · Nonesterified free fatty acids

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## Introduction

Pediatric obesity rates in the United States have shown a well-defined disparity by ethnicity, where 42 % of Latinos, 41 % of African Americans (AAs), and 30 % of Caucasians between 12–19 years of age were classified as overweight or obese [1]. Interestingly, Native American (NA) adolescents have been shown to have a higher prevalence of obesity than all other races combined [2, 3]. For those of NA and Latino descent, ethnic disparities in obesity rates emerge early in life and have profound consequences on metabolic health [2, 4] as shown by their high prevalence of prediabetes and type 2 diabetes mellitus (T2DM) [3, 5, 6, 7•, 8]. As a result of high rates of obesity and diabetes risk, practitioners and researchers are faced with finding appropriate treatment/prevention options for prediabetes and T2DM in ethnically diverse youth. In this regard, the Treatment Options for Type 2 Diabetes in Adolescents and Youth found that metformin treatment in children had an overall failure rate of 45.6 % and an even higher failure rate of 52.8 % in AAs [9•]. This study exemplifies the need for a more complete understanding of the ethnic-specific pathophysiology underlying the progression from normal glucose tolerance to pre-diabetes and diabetes in order to effectively prevent and treat T2DM across an ethnically diverse population. In the current review, we examine studies that have contributed to our understanding of prediabetes and T2DM in overweight and obese youth from various ethnic groups. Although the literature is limited by an inconsistency in the terminology used for various ethnicities, we synthesized important ethnic-specific advances by using Caucasian for any study using the terms Caucasian, White, or non-Hispanic White; Latino to describe people of Hispanic, Latino, or Mexican-American descent; AA to describe people of African, AA or Black-Caribbean descent; Asian to describe people of Asian, South Asian, East Asian, Southeast Asian descent, or other specific Asian ethnicity, and NA to describe people of

American Indian, Pima Indian, Aboriginal, First Nation, or Alaska Native ethnicity. We also recognize that there may be variation within these subgroups; however, this is an understudied area and beyond the scope of this review.

## Ethnic Differences in Prediabetes and T2DM

Recent NHANES data show that AA children have the lowest prevalence of prediabetes while Caucasians and Latinos have the highest [10]. Compared with other ethnicities, AA, Latino, and NA children have the highest rates of T2DM [6, 11]. Although Asian children have not been widely recognized as having an elevated risk for diabetes, a recent study in Asian adults reported that prevalence rates of diabetes surpassed that in AAs, Latinos, and NAs [12•]. Among NA children, 1 study has found that the total number of young NAs diagnosed with diabetes increased by 71 % between 1990 and 1998 [13]. Due to the observed ethnic differences in risk for prediabetes and T2DM, current studies have begun to further characterize ethnic specific alterations in insulin secretion and sensitivity seen during obesity. At the same time that these disparities are being considered, novel research examining ectopic fat accumulation, adipose tissue inflammation/fibrosis, and the toxic effect of nonesterified free fatty acids (NEFA) are being examined as potential factors contributing to higher rates of prediabetes and T2DM in minority youth.

## Ethnic Differences in Insulin Secretion and Sensitivity in Overweight and Obese Youth

Ethnic differences in diabetes risk in overweight and obese youth have been well documented, where, independent of overall adiposity, minority children exhibit more severe insulin resistance but an enhanced insulin secretory response when compared with Caucasian children [4, 14]. A recent study, using a hyperglycemic clamp technique, supports these observations; the authors observed that compared with Caucasian youth, overweight AAs had up to a 75 % higher insulin secretion relative to their insulin sensitivity, indicating increased or upregulated β-cell responsiveness [14]. In more recent work from our group, we confirmed that obese AA adolescents had 41.7 % lower insulin sensitivity, but a 63 % higher acute insulin response (AIR) compared with obese Latinos. Interestingly, the hyperinsulinemic response to intravenous glucose that has been observed in AAs was not detected in response to an oral glucose challenge [15]. Unfortunately, no studies in Asian children have thoroughly examined T2DM risk, but one recent study found that adiposity markers were positively associated with insulin resistance and these associations were strongest in Asians followed by AAs and Caucasians [16••]. It has also been shown that like AAs, NA adults have a robust insulin response to glucose; however, NAs exhibit a lower insulin sensitivity hence increasing their risk for T2DM [17]. It is unknown whether these findings hold true in NA children. Collectively, these studies show ethnic differences in insulin resistance and secretion in overweight and obese youth that should be examined using various methodologies.

## Subcutaneous and Visceral Adipose Tissue

At similar levels of body fat mass, minority youth are more insulin-resistant and at an increased risk for diabetes compared with Caucasians. Recent studies suggest that body fat distribution, and not overall adiposity, may explain this phenomenon. In this regard, studies in children and adolescents have shown positive associations between increased subcutaneous abdominal adipose tissue (SAT) and visceral adipose tissue (VAT) with fasting insulin levels and markers of insulin resistance [16••, 18•, 19••, 20, 21, 22••, 23, 24]. However, it is unlikely that these relationships fully account for ethnic differences in insulin resistance since AAs have the lowest levels of VAT, [20, 25, 26] yet are more insulin resistant than Caucasians and Latinos [4]. In addition, although obese NAs are more insulin-resistant than equally obese Caucasians, these two groups have been shown to have similar levels of VAT that are unrelated to insulin action and secretion [27]. SAT is another fat depot that is thought to contribute to insulin resistance due to its larger volume and functional characteristics, making it more susceptible to inflammation and subsequent deposition of ectopic fat [28–32]. Furthermore, abdominal SAT has 2 distinct compartments, the deep SAT (dSAT) and superficial SAT (sSAT) depots that differ in their contribution to metabolic disease risk [33, 34]. For example, a study in lean and obese adults found that dSAT and VAT, but not sSAT, were inversely correlated with insulin-stimulated glucose utilization as measured by euglycemic clamp [33]. At the same time, recent studies have identified ethnic differences in the distribution of dSAT and sSAT [35–38] where it has been shown that Asians have the lowest BMI, yet the largest accumulation of VAT and dSAT with increasing adiposity when compared with Caucasian, AA, and Latino adults [36]. In another study, NA and Asian adults were shown to have significantly higher amounts of dSAT compared with Caucasians [35]. Our review of the literature did not yield any reports examining dSAT in children or adolescents; however, adult studies suggest that ethnic differences in dSAT and sSAT could partially explain ethnic differences in insulin sensitivity and secretion in youth.

## Ectopic Fat: Intramyocellular Lipid

Intramyocellular lipid (IMCL) has been found to be associated with insulin resistance and vary by ethnicity in overweight and

obese youth (Table 1) [20, 22••, 39•, 40, 41]. A previous study found that among severely obese adolescents, increased IMCL and intraperitoneal fat were significant predictors of impaired glucose tolerance [39•]. When comparing youth from various ethnic groups, a recent report has shown that AAs and Latinos have more IMCL than Caucasians, even after controlling for BMI and VAT [20]. Interestingly, a study in AA, Latino and Caucasian children, found that IMCL was inversely associated with adiponectin and positively associated cardiovascular risk factors; however, a majority of these relationships were abolished after controlling for BMI, SAT, or VAT [42•], suggesting that VAT and/or ectopic fat may be more strongly associated with metabolic disturbances [21, 22••]. To our knowledge, there are no studies examining IMCL in NA or Asian children; however, 1 study in Asian and Caucasian men found that after matching on age and BMI, Asians had higher IMCL compared with Caucasians, but unlike Caucasians, IMCL in Asians was not related to insulin sensitivity or obesity [40]. Another study in NA adults found that IMCL did not predict reduced insulin-mediated suppression of hepatic glucose production or insulin-mediated glucose disposal [43]. These studies suggest that increases in IMCL may contribute to insulin resistance in an ethnic-specific manner; however, the documented correlation between IMCL, SAT, VAT, and liver fat make it difficult to tease apart the exact influence of each fat depot [20, 22••, 42•, 44]. Additional studies comparing the contribution of IMCL, SAT, and VAT are warranted as a means to possibly explain observed ethnic differences in metabolic disease risk in youth.

**Table 1** Ectopic fat depots and risk for T2DM in youth and adults

| | Insulin resistance | Insulin secretion[c] |
|---|---|---|
| Ectopic fat depot | AAs > Latinos > Caucasians [4]<br>AAs > Caucasians [14]<br>AAs ≈ Asians > Caucasians [94][a]<br>NAs > AAs [17][a] | Latinos > AAs ≈ Caucasians [4]<br>AAs > Caucasians [14]<br>AAs > Asians ≈ Caucasians [94][a]<br>NAs ≈ AAs [17][a] |
| Intramyocellular Lipid (IMCL) | | |
| AAs ≈ Latinos > Caucasians [20]<br>Asians > Caucasians [40][a] | • Ethnically diverse: 1 study found no relationship between IMCL and SI [22••] while the other found and inverse association [41]<br>• Asians: IMCL not associated with SI [40][a]<br>• Caucasians and AAs: intralipid infusion increased IMCL and decreased liver and peripheral SI; no ethnic difference [95] | Ethnically diverse: one study found IMCL was not associated with fasting insulin [22••], whereas the other found a positive association between intramuscular adipose tissue and OGTT-insulin area under curve [41] |
| Liver Fat (LF) | | |
| Latinos > Caucasians > > AAs [19••, 25, 51]<br>Asians > > Caucasians [38][a] | • Caucasians: LF associated with 55 % ↓ SI [50•]<br>• Caucasians, AAs, Asians: NAFLD associated with 150 % ↑ HOMA-IR [23]<br>• Latinos: high LF (>5 %) associated with 75 % ↓ SI, 60 % ↑ HOMA-IR [49•]<br>• Latinos: high LF associated with 24 % ↓ SI [55••]<br>• 22 AAs: high LF associated with 49 % ↓ SI [55••]<br>• AAs and Latinos (Prediabetic vs NGT): have 30 % ↑ LF; no ethnic difference [19••]<br>• Caucasians and NAs with T2DM: LF negatively associated with SI [48] | • Caucasians: LF not associated with AIR [50•]<br>• Caucasians, AAs, and Asians: NAFLD associated with 30 % ↓ DI [23]<br>• Latinos: high LF (>5 %) associated with 31 % ↑ AIR [49•]<br>• Latinos: high LF associated with 31 % ↑ AIR [55••]<br>• AAs: high LF associated with 42 % ↓ DI [55••] |
| Pancreatic Fat (PF) | | |
| Latinos > AAs [47•][b]<br>Latinos ≈ Caucasians > > AAs[a] [46] | • AAs and Latinos (Prediabetic vs NGT): have 31 % ↑ PF [19••]<br>• AAs (Prediabetic vs NGT): 63 % ↑ PF [19••]<br>• Latinos (Prediabetic vs NGT): no difference in PF [19••]<br>• AAs and Latinos: PF not associated with SI [47•][b] | • Caucasians and AAs: PF associated with AIR [46][a]<br>• Latinos: PF not associated with AIR [46][a]<br>• AAs and Latinos: PF not associated with AIR or DI [47•][b] |

*AIR* acute insulin response, *DI* disposition index, *IMCL* intramyocellular lipid, *LF* liver fat, *PF* pancreatic fat

[a] Adults

[b] Young adults (13–25 years)

[c] Refers to insulin secretion or AIR

### Ectopic Fat: Liver and Pancreatic Fat

Studies have emerged that suggest that ethnic differences in insulin sensitivity and secretion may be directly due to differences in liver and pancreatic fat accumulation (Table 1) [19••, 38, 45, 46, 47•]. Numerous studies have documented an association between high liver fat and reduced insulin sensitivity and β-cell function [19••, 23, 48, 49, 50•], while other reports have shown that Latinos have the most liver fat, followed by Caucasians and AAs [19••, 25, 51]. In a previous study of Caucasian healthy weight, overweight, and obese adolescents, those with hepatic steatosis had a 55 % lower insulin sensitivity and a 2-fold greater prevalence of metabolic syndrome compared with those without hepatic steatosis [50•]. Further supporting these findings, a study in Canadian Caucasian and NA adolescents found that those with T2DM had higher liver fat compared with those without T2DM and liver fat was negatively associated with insulin sensitivity [48]. Supporting these findings, another study in Caucasian, AA, and Asian adolescents found that obese adolescents with nonalcoholic fatty liver disease (NAFLD) had a 30 % lower disposition index (DI) compared with those who were obese and without NAFLD [23]. Our group has shown similar relationships in obese Latino adolescents, where those with elevated liver fat (>5 % by MRI) had a tendency ($P$=0.06) for a 75 % lower insulin sensitivity and a 71 % higher AIR compared with those with low liver fat [49•]. These results suggest that liver fat is associated with metabolic abnormalities in obese youth from various ethnic groups. However, liver fat has been shown to be highly correlated with VAT, making it difficult to tease apart its independent contributions to metabolic dysfunction [52, 53]. In an effort to address this issue, our group examined associations between liver fat and VAT with risk factors for T2DM in obese AA and Latino adolescents using measures from a frequently sampled intravenous glucose tolerance test (FSIVGTT) with minimal modeling. We found that liver fat, not VAT, was inversely associated with insulin sensitivity and the effect of high liver fat (>5.5 %) compared with low liver fat (<5.5 %) was more pronounced in AAs compared with Latinos. Specifically, in Latinos high liver fat was associated with a 24 % lower insulin sensitivity, 31 % higher AIR, and was not associated with DI. In AAs, high liver fat was associated with a 49 % lower insulin sensitivity, was not associated with AIR, and was associated with 42 % lower DI. These results suggest a failure of compensatory insulin secretion and/or clearance in response to liver fat associated insulin resistance in AAs but not Latinos [54, 55••, 56]. Since similar studies have not been performed in children belonging to other ethnicities, it is unknown how liver and/or VAT contribute to risk for T2DM in overweight and obese NA, Asian or Caucasian children.

There are a handful of findings that support an independent contribution of pancreatic fat to metabolic disease risk [19••, 46, 57•]. When comparing Caucasian, AA, and Latino adults with similar levels of adiposity, Latinos have a 2-fold higher pancreatic fat fraction compared with AAs [46, 47•] while Latinos and Caucasians have similar levels of pancreatic fat [46]. A recent study in AA, Latino, and Caucasian adults suggests that pancreatic fat has the potential to be used as a biomarker for pancreatic β-cell dysfunction, especially in Latinos [46]. Studies examining pancreatic fat in youth of various ethnicities are limited while there are no studies in Asians or NAs. In AAs and Latinos, we have shown racial differences in pancreatic fat in overweight and obese adolescents and young adults [19••, 47•]. Specifically, in overweight and obese AA and Latino adolescents, we found that those with prediabetes have a 30 % higher liver fat and 31 % higher pancreatic fat compared with those with normal glucose tolerance. We also found that pancreatic fat predicted prediabetes in AAs whereas liver fat predicated prediabetes in Latinos [19••]. These results suggest that liver fat is associated with metabolic abnormalities in obese Latinos while pancreatic fat may play a larger role in AAs. Given that VAT, liver fat, and pancreatic fat are highly correlated [47•], future studies should aim to examine all of these fat depots in obese youth in an effort to elucidate the exact contributions of each fat depot to insulin resistance and β-cell dysfunction.

### Adipose Tissue Inflammation and Fibrosis

Studies also show that metabolic activity, inflammation, and fibrosis in fat may play a role in risk for T2DM. Specifically, studies have shown that obesity is associated with a state of chronic low-grade inflammation that is correlated with decreased insulin sensitivity and impaired glucose metabolism [58•, 59•, 60–62]. Although it was once believed that adipose tissue was only involved in the storage of free fatty acids as triglycerides, it is now recognized that this tissue also acts as a dynamic endocrine organ, contributing to the chronic-low grade inflammation seen during obesity. For instance, during excess weight gain there is a marked increase in adipose tissue inflammation and fibrosis, which have been shown to be associated with insulin resistance seen during obesity [63]. Although few studies have performed adipose tissue biopsies in children, plasma markers of inflammation have been shown to be strongly associated with risk for T2DM in overweight and obese youth from various ethnic backgrounds. For example, a study in boys found that those who were overweight had higher serum levels of interleukin (IL)-6, IL-8, interferon-γ, monocyte chemoattractant protein (MCP)-1, and c-reactive protein (CRP) compared with those of normal weight [64]. Among Mexican children, those suffering from obesity have been shown to have higher levels of CRP and IL-1β compared with nonobese [60]. Another study in AA and Latino peripubertal females demonstrated that CRP was positively

related to BMI, percent body fat, fasting insulin, and AIR as well as negatively correlated with insulin sensitivity [58•]. One of the few recent studies including Asian children found that, after controlling for adiposity, Asians had higher levels of CRP, A1c, and insulin levels compared with white Caucasian and AA children [62]. To our knowledge, there is only one study examining inflammation in NA children. This study found elevated levels of CRP that were associated with increased adiposity, insulin resistance, worsening lipid profile, and decreased adiponectin levels [65]. Findings from these studies are especially important due to the high incidence of childhood obesity, making it likely that these children are exposed to chronic levels of low-grade inflammation from an early age into adulthood.

In light of the strong associations between plasma markers of inflammation and risk for T2DM in overweight and obese children, recent studies involving adipose tissue biopsies in young adults are of significant interest. Specifically, SAT biopsies performed in Caucasian, AA, Latino, and NA adults have shown that, in addition to elevations in plasma markers of inflammation, increases in proinflammatory immune cells in adipose tissue and elevated levels of fibrosis are associated with systemic and local inflammation [66–69]. In another study by our group, we assessed SAT inflammation by the presence of crown-like structures (CLS) in obese AA and Latino young adults. We found that those with SAT inflammation had greater levels of VAT, liver fat, tumor necrosis factor (TNF)-α, fasting insulin and glucose, and a lower DI than those without SAT inflammation [66]. As previously mentioned, studies examining SAT inflammation and fibrosis are limited in children; however, 1 study in obese youth observed macrophages and lymphocytes in perivascular positions in the adipose tissue [70] while another study in children found macrophages in the SAT of normal weight, overweight, and obese children as young as 5 years of age [71•]. Finally, unpublished work from our group has shown that the amount of collagen present in the SAT of obese Italian children was inversely correlated with DI. Results from these studies suggest that immune cells interact with extracellular matrix remodeling at an early age [71•] and that additional work in needed to understand how SAT inflammation and fibrosis contribute to obesity associated insulin resistance and decreased β-cell function in overweight and obese youth. Future work should aim to characterize the immune cells and fibrosis present in overweight and obese youth in order to determine their contribution to observed ethnic differences in insulin sensitivity and secretion.

## Elevated Plasma Nonesterified Fatty Acids (NEFA)

Studies in obese adults have documented clear relationships between decreased insulin suppression of lipolysis in adipose tissue, NEFA, and T2DM [72]. A recent study in obese youth has shown that those with and without T2DM have impaired suppression of lipolysis [73•]. Given that increased liver fat, IMCL [74, 75], and inflamed [76] and fibrotic adipose tissue [77] are associated with increased whole body insulin resistance, it is possible that NEFA are the link between ethnic differences in ectopic fat, inflammation, and risk for T2DM. Studies in overweight and obese youth have observed elevations in fasting NEFA and NEFA levels after an oral glucose or intravenous lipid challenge. Salgin et al. reported data from a longitudinal study where higher fasting NEFA were associated with a lower insulin secretion following a 30-minute oral glucose challenge in children with normal glucose tolerance (NGT); however, racial or ethnic differences were not assessed [78•]. The earliest work in this field with regard to ethnicity showed that, after an intravenous lipid infusion, elevations in NEFA were associated with increased insulin resistance in AA and Caucasian adolescents [79]. The authors noted that ethnicity did not modify the relationship between NEFA and insulin resistance, which was surprising given that AAs have a lower insulin sensitivity than Caucasians [79]. In contrast, among female children and adults, another study reported ethnic differences in NEFA during an FSIVGTT where, independent of insulin secretion, AAs had lower NEFA than Caucasians [20, 80]. The physiologic implications of this finding is still unclear and warrants further study. In recent studies, elevated NEFA have been shown to contribute to increased insulin resistance in youth. In 1 such study, overweight and obese AA and Caucasian children exposed to an intralipid infusion showed decreased insulin secretion and β-cell function when compared with those in the control group [81••]. Using data from our lab, we have shown that when compared with those with NGT, Latino children with prediabetes had higher fasting NEFA that were also inversely related to β-cell function [82•]. Our findings suggest that elevated NEFA in youth may already translate to declines in β-cell function. Although these associations do not demonstrate causality, they suggest possible ethnic-specific roles of NEFA in T2DM pathophysiology. To our knowledge, there are no studies examining these relationships in Asian or NA children, warranting their inclusion in future studies.

## Ethnic Differences in Insulin Sensitivity and Secretion as a Function of Glycemic Status

Despite established differences in T2DM risk among minority children, few studies address the use of hyperglycemic markers of T2DM among ethnically diverse groups of overweight and obese youth. Historically, impaired fasting glucose and impaired glucose tolerance have been used to diagnose prediabetes based on their relationship with decreased insulin sensitivity, altered insulin secretion, and β-cell dysfunction.

**Table 2** Ethnic differences in hyperglycemic markers and metabolic indices in youth

| | Hyperglycemic marker | Metabolic indices |
|---|---|---|
| Latinos ($n$=206) [83••][b] | 6 %–6.4 % vs <6.0 % | 21 % ↓ SI<br>30 % ↓ Insulin Secretion<br>31 % ↓ DI |
| | 5.7 %–6.4 % vs <5.7 % | ≈ SI<br>≈ AIR<br>≈ DI |
| Caucasians and AAs ($n$=204) [84••][c] | 5.7 %–6.4 % vs <5.7 % | 18 % ↓ SI<br>30 % ↓ GDI |
| Caucasians and AAs ($n$=223) [87•][c] | ≥90–99 mg/dL vs <90 mg/dL fasting | ≈ SI<br>↓ Insulin Secretion<br>23 % ↓ GDI[d] |
| Caucasians and AAs ($n$=113) [88][c] | ≥155 mg/dL vs <155 mg/dL at 1 h post-OGTT | ≈ SI<br>≈ Insulin Secretion<br>35.5 % ↓ GDI[d] |
| Caucasians ($n$=1454) [90] | ≥132 mg/dL vs <132 mg/dL at 1 h post-OGTT | ↓ DI[e] |
| Latinos<br>($n$=233, 9-y longitudinal) [89••][b] | ≥155 mg/dL vs <155 mg/dL at 1 h post OGTT | ≈ SI<br>↓ Insulin Secretion<br>↓ DI |
| Caucasians and AAs ($n$=147) [91][a,c] | ≥120 mg/dL vs <120 mg/dL at 2 h post OGTT | ≈ SI<br>≈ Insulin Secretion<br>40 % ↓ GDI[d] |
| Caucasians, nondiabetic<br>($n$=60, 2-y longitudinal) [92••][c] | 120–139 mg/dL vs 100–119 vs<br><100 mg/dL at 2 h post OGTT | ↓ SI<br>↓ Insulin Secretion |

*AIR* acute insulin response, *DI* disposition index, SI insulin sensitivity

[a] Study included nondiabetic and diabetic children

[b] Studies used frequently sampled intravenous glucose tolerance test (FSIVGTT) with minimal modeling

[c] Studies compared hepatic and peripheral insulin sensitivity by [6,6-$^2$ $H_2$] glucose and a 3 h hyperinsulinemic-euglycemic clamp and β-cell function by a 2 h hyperglycemic clamp (~225 mg/dL)

[d] Glucose disposition index (GDI) was expressed relative to insulin sensitivity (GDI = SI * first-phase insulin)

[e] DI was calculated from a regression equation using data from an OGTT

Recently, A1c has been recommended as an additional criterion for the diagnosis of prediabetes and T2DM [54, 56]; however, there are only 2 recent studies examining how various A1c thresholds are associated with β-cell dysfunction in children. As shown in Table 2, these studies include overweight Latino children or overweight AA and Caucasian youth. Using data from a FSIVGTT and minimal modeling, we showed that Latino children with an A1c of 6.0-6.4 % had 21 % lower insulin sensitivity and 30 % lower insulin secretion compared with those with A1c <6.0 % [83••]. Using various clamp methodologies, the other study found that Caucasian and AA children with an A1c in the range of 5.7 %–6.4 % had a lower insulin sensitivity and β-cell function compared with those with an A1c below 5.7 %, a threshold recommended by the American Diabetes Association [84••]. Since these results were independent of ethnicity, these findings suggest that the A1c threshold was adequate for either AA or Caucasian overweight youth. In our study, although Latino children within the range of 5.7 %–5.9 % exhibited a lower insulin sensitivity and β-cell function compared with those below 5.7 %, this difference did not reach statistical significance [83••]. To our knowledge, there are no studies examining A1c in Asians. A recent study in Canadian children found that A1c levels at the time of T2DM diagnosis were significantly higher among NAs than Caucasians (~10.1 % vs 8.7 %) [85•]. These studies suggest that A1c thresholds for diagnoses of T2DM may differ by ethnicity; therefore, studies specifically aimed at testing ethnic

**Table 3** Summary of key points

- Ethnic-driven differences should be considered when establishing new criteria (eg, 1- and 2-h glucose, A1c) for diagnoses of prediabetes and T2DM.
- Studies suggest that liver and pancreatic fat play a central role in metabolic dysfunction and the importance of these depots differ by ethnicity.
- Adipose tissue inflammation and fibrosis may offer new insights into ethnic differences in insulin sensitivity and secretion.
- The limited data in Asian and Native American youth warrant inclusion of these groups in studies aiming to understand the underlying pathophysiology of T2DM.

differences in the usage of A1c as a diagnostic criterion are warranted.

In addition to A1c, recent studies have examined various fasting, 1-hour, and 2-hour glucose thresholds and how they relate to risk for T2DM in children. As mentioned previously, these investigations are limited by their inability to directly examine ethnic differences among AAs, Latinos, Caucasians, and Asians. As shown in Table 2, studies have examined glucose thresholds for assessing β-cell dysfunction in only (1) Caucasian (2) Latino or (3) Caucasian and AA children. For instance, AAs with T2DM have been shown to have increased insulin secretion and β-cell function compared with Caucasian children with T2DM [86]. Although these results exemplify the need to consider ethnic differences in insulin secretion in those with overt metabolic disease using either fasting or postprandial glucose, there are no studies comparing these relationships to Asian or Latino children with T2DM. In the handful of studies that included AA and Caucasian youth, direct ethnic comparisons were not assessed. From these studies, varying fasting and 1-hour glucose cut-points were found to be associated with decreased β-cell function [87•, 88, 89••, 90]. In Caucasian children, a 1-hour OGTT glucose value of 132 mg/dL or greater was associated with decreased β-cell function while among Latinos, the threshold was found to be higher at 155 mg/dL. Although it has not been determined if these thresholds are optimal for each ethnicity, these results suggest that further study is warranted. Using 2-hour glucose cut-offs, a cross-sectional study in overweight AA and Caucasian children and a longitudinal study in Italian children found that insulin sensitivity and secretion was significantly lower in participants with a blood glucose level of 120 mg/dL, which is 20 mg/dL lower than the current threshold for impaired glucose tolerance [91, 92••]. In addition to these glycemic indices, we have shown that overweight Latinos with a biphasic glucose response curve to an oral glucose challenge have a lower insulin sensitivity and secretion compared with those with a monophasic response curve [93•]. Considering the ethnic compositions of each of these studies, findings are difficult to interpret in regards to how they should be used clinically. This observation further highlights the need for studies to directly compare these glycemic cut-points in overweight and obese Caucasian, AA, Latino, and Asian youth.

## Conclusions (Table 3)

Determinants of insulin sensitivity and secretion may help explain ethnic-specific differences in T2DM risk in children and youth. The use of A1c for clinical diagnosis, along with other hyperglycemic thresholds for fasting and post-OGTT, have demonstrated their utility by elucidating ethnic disparities in insulin sensitivity and secretion. Studies investigating ethnic differences in ectopic fat accumulation, such as SAT, VAT, IMCL, liver, and pancreatic fat, have the potential to explain some of the observed ethnic differences in insulin resistance, altered insulin secretion, and risk for diabetes by uncovering differential deposition of ectopic fat that may directly contribute to insulin resistance and β-cell dysfunction. Studies examining adipose tissue inflammation and fibrosis suggest that not only the location, but also the inflammatory state and extracellular matrix of the adipose tissue may contribute to disease risk in an ethnic-specific manner. Given the established associations between insulin resistance, elevated levels of NEFA, and risk for T2DM, future studies should aim to determine whether differing patterns of ectopic fat accumulation, inflammation, or NEFA metabolism drive ethnic differences in insulin sensitivity and secretion. In light of recent studies, an improved understanding of obesity-associated risk for diabetes in youth will likely lead to differential behavioral and/or pharmacologic treatments to address ethnic differences in the underlying pathophysiology of this disease.

### Compliance with Ethics Guidelines

**Conflict of Interest** T. L. Alderete declares that she has no conflict of interest. C. M. Toledo-Corral declares that she has no conflict of interest. M. I. Goran declares that he has no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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