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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 non-esterified 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; Non-Alcoholic Fatty Liver Disease; Pancreatic Fat; Adipose Tissue Inflammation; Adipose Tissue Fibrosis; Nonesterified Free Fatty Acids

Introduction

Pediatric obesity rates in the United States show a well-defined disparity by ethnicity, where 42% of Latinos, 41% of African-American (AA), and 30% of Caucasians between 12–19

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Disclosure

No potential conflicts of interest relevant to this article were reported.

Compliance with Ethics Guidelines

Conflict of Interest

TL Alderete, CM Toledo-Corral, and MI Goran declare that they have 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.

years of age were classified as overweight or obese [1]. Native American (NA) adolescents have a higher prevalence of obesity than those in 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; African-American (AA) to describe people of African, African-American or Black-Caribbean descent; Asian to describe people of Asian, South Asian, East Asian, Southeast Asian descent or other specific Asian ethnicity and Native American 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 sub-groups; 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 to 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 AA, Latinos, and NAs [12•]. Among NA children, one study has found that the total number of young NAs diagnosed with diabetes increased by 71% between 1990 to 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 non-esterified 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 to Caucasian children [4, 14]. A recent study, using a hyperglycemic clamp technique, supports these observations; the authors observed that compared to Caucasian youth, overweight AAs have up to a 75% higher insulin secretion relative to their insulin sensitivity, an indicator of increased or up-regulated 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 to 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

Although non-Caucasian children and youth appear to be more insulin resistant, independent of obesity, a variety of studies have recently examined the role of body fat distribution in explaining this phenomenon. Studies in children and adolescents show 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•–24]. However, these relationships do not necessarily explain ethnic differences in insulin resistance, since AAs have lower levels of VAT than Caucasians and Latinos [20, 25, 26] yet are more insulin resistant [4]. Additionally, increases in VAT in NA adults do not explain insulin resistance and hyperinsulinemia when compared to equally obese Caucasians [27]. Although some studies suggest that VAT plays a larger role in the development of insulin resistance, other studies in adults suggest that SAT has a significant impact due to its larger volume and functional characteristics, making it more susceptible to inflammation and subsequent deposition of ectopic fat [28–32]. Abdominal SAT has two 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 sSAT and dSAT [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 to Caucasian, AA, and Latino adults [36]. In another study, NA and Asian adults were shown to have significantly higher amounts of dSAT when compared to Caucasians [35]. Our review of the literature did not yield any reports examining dSAT in children and 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•–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 AAs, 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, one study in Asian and Caucasian men found that after matching on age and BMI, Asians had higher IMCL compared to Caucasians, but unlike Caucasians, IMCL in Asians was not related to insulin sensitivity or obesity [40]. Another study in adult NAs 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.

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, 45–47•]. Numerous studies have documented an association between high liver fat and reduced insulin sensitivity and β-cell function [19••, 23, 48–50•], 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 twofold greater prevalence of metabolic syndrome compared to 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 to 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 non-alcoholic fatty liver disease (NAFLD) had a 30% lower disposition index (DI) compared to 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 to 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 the association

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 to low liver fat was more pronounced in AAs compared to 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 Caucasians, AAs, and Latino adults with similar levels of adiposity, Latinos have a two-fold higher pancreatic fat fraction compared to 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, as 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 to 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, 61, 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 there are no studies in children involving adipose tissue biopsies, studies using plasma markers of inflammation have found strong associations 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 to those of normal weight [64]. Among Mexican children, those suffering from obesity have been shown to have higher levels of CRP and IL-1β when compared to non-obese [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 to 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 pro-inflammatory 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, one 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 five 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 is 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 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 Non-Esterified Fatty Acids (NEFA)

Studies in obese adults have documented a relationship 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 [79] first showed that after an intravenous lipid infusion, elevations in NEFA were associated with increased insulin resistance in AA and Caucasian adolescents. 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, another study reported ethnic differences in NEFA during an FSIVGTT where, independent of insulin secretion, AA women and girls had lower NEFA than Caucasian women and girls [20, 80]. The physiologic implications of this finding are still unclear and warrant further study. In recent studies, elevated NEFA haven been shown to contribute to increased insulin resistance in youth. In one such study, overweight and obese AA and Caucasian children exposed to an intralipid infusion showed decreased insulin secretion and β-cell function when compared to those in the control group [81••]. Using data from our lab, we have shown that when compared to 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 ethnicity-associated 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. Recently, A1c has been recommended as an additional criterion for the diagnosis of prediabetes and T2DM [54, 56]; however, there are only two 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 an 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 when compared to 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 to those with an A1c below 5.7%, a threshold recommended by the American Diabetes Association [84••]. Their results were independent of ethnicity, suggesting 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 when compared to 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 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, recent studies have examined glucose thresholds for assessing β-cell dysfunction in either: 1) Caucasian only, 2) Latino only, or 3) Caucasian and AA children. For instance, AAs with T2DM have been shown to have increased insulin secretion and β-cell function when compared to 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 post-prandial 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 one-hour glucose cut-points were found to be associated with decreased β-cell function [87•, 88, 89••, 90]. A 1-hr OGTT cut-off showed that in Caucasian children, a threshold of 132 mg/dL was associated with decreased β-cell function while another study, in both Caucasians and Latinos, found the threshold to be higher at 155 mg/dL. It has not been determined if these thresholds are the optimal for each ethnicity, but the results suggest that further study is warranted. Using the 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 when compared to 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/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 function. 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 and inflammation 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.

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• Of importance

•• Of major importance

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Table 1

Ectopic Fat Depots and Risk for T2DM in Youth and Adults

Ectopic Fat Depot	Insulin Resistance **AAs > Latinos > Caucasians [4]** **AAs > Caucasians [14]** **AA ≈ Asian > Caucasian [94]§** **NAs > AAs [17]§**	Insulin Secretion* **Latinos > AAs ≈ Caucasians [4]** **AAs > Caucasians [14]** **AA > Asians ≈ Caucasians [94]§** **NAs ≈ AAs [17]§**
Intramyocellular Lipid (IMCL)		
AAs ≈ Latinos > Caucasians [20] Asians > Caucasians [40]§	• Ethnically diverse: one study found no relationship between IMCL & SI [22••] while the other found and inverse association [41] • Asians: IMCL not associated with SI [40]§ • Caucasians & AAs: intralipid infusion increased IMCL & decreased liver & peripheral SI; no ethnic difference [95]	• Ethnically diverse: one study found IMCL was not associated with fasting insulin [22••] while 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] Asians ≫ Caucasians [38]§	• Caucasians: LF associated with 55% ↓ lower SI [50•] • Caucasians, AA, Asians: NAFLD associated with 150% ↑ HOMA-IR [23] • Latinos: high LF (>5%) associated with 75% ↓ SI, 60% ↑ HOMA-IR [49•] • Latinos: high LF associated with 24% ↓ SI [55••] • 22AAs: high LF associated with 49% ↓ SI [55••] • AAs & Latinos (Prediabetic vs. NGT): have 30% ↑ LF; no ethnic difference [19••] • Caucasians & NAs with T2DM: LF negatively associated with SI [48]	• Caucasians: LF not associated with AIR [50•] • Caucasians, AAs, & Asians: NAFLD associated with 30% ↓ DI [23] • Latinos: high LF (>5%) associated with 31% ↑ AIR [49•] • Latinos: high LF associated with 31% ↑ AIR [55••] • AAs: high LF associated with 42% ↓ DI [55••]
Pancreatic Fat (PF)		
Latinos ≫ AAs[7] Latinos ≈ Caucasians ≫ AAs§ [46]	• AAs & Latinos (Prediabetic vs. NGT): have 31% ↑ PF [19••] • AAs (Prediabetic vs. NGT): 63% ↑ PF [19••] • Latinos (Prediabetic vs. NGT): no difference in PF [19••] • AAs & Latinos: PF not associated with SI [47•]§§	• Caucasians & AAs: PF associated with AIR [46]§ • Latinos: PF not associated with AIR [46]§ • AAs & Latinos: PF not associated with AIR or DI [47•]§§

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

§Adults;

§§ Young adults (13–25 years)

* Refers to insulin secretion or AIR.

Table 2

Ethnic Differences in Hyperglycemic Markers and Metabolic Indices in Youth

	Hyperglycemic Marker	Metabolic Indices
Latino (n=206) [83••][b]	6–6.4% vs. <6.0%	21% ↓ SI 30% ↓ Insulin Secretion 31% ↓ DI
	5.7–6.4% vs. <5.7%	≈ SI ≈ AIR ≈ DI
Caucasian & AA (n=204) [84••][c]	5.7–6.4% vs. <5.7%	18% ↓ SI 30% ↓ GDI
Caucasian & AA (n=223) [87•][c]	≥90–99 mg/dL vs. <90 mg/dL fasting	≈ SI ↓ Insulin Secretion 23% ↓ GDI[d]
Caucasian & AA (n=113) [88][c]	≥155 mg/dL vs. <155 mg/dL at 1-hr post OGTT	≈ SI ≈ Insulin Secretion 35.5% ↓ GDI[d]
Caucasian (n=1,454) [90]	≥132 mg/dL vs. <132 mg/dL at 1-hr post OGTT	↓ DI[e]
Latino (n=233, 9-yr longitudinal) [89••][b]	≥155 mg/dL vs. <155 mg/dL at 1hr post OGTT	≈ SI ↓ Insulin Secretion ↓ DI
Caucasian & AA (n=147) [91][a,c]	≥120 mg/dL vs. <120 mg/dL at 2-hr post OGTT	≈ SI ≈ Insulin Secretion 40% ↓ GDI[d]
Caucasian, non-diabetic (n=60, 2-yr longitudinal) [92••][c]	120–139 mg/dL vs. 100–199 vs. <100 mg/dL at 2-hr post OGTT	↓ SI ↓ Insulin Secretion

[a] Study included non-diabetic and diabetic children;

[b] Studies used FSIVGTT with minimal modeling (Disposition index [DI] = insulin sensitivity [SI] * acute insulin response [AIR]);

[c] Studies compared hepatic and peripheral insulin sensitivity by [6,6-$^2H_2$] 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.

Table 3

Summary of Key Points

- Ethnic-driven differences should be considered when establishing new criteria (e.g., 1- and 2-hour 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.