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PEDIATRIC OBESITY AND INSULIN RESISTANCE: ENDOCRINE MECHANISMS AND RISK OF CHILDHOOD DIABETES

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ABSTRACT

Background: Pediatric obesity is a growing public health crisis in Pakistan, yet region-specific data linking adipose endocrine dysfunction to insulin resistance and type 2 diabetes mellitus (T2DM) risk remain limited. This study investigated the endocrine mechanisms driving insulin resistance in obese children within the urban population of Islamabad, Pakistan. **Methods**: A cross-sectional analytical study was conducted from January 2024 to December 2025 at two tertiary care centers in Islamabad. Participants aged 8–16 years were stratified into overweight/obese ($n = 195$) and normal-weight control ($n = 187$) groups based on WHO growth standards. Anthropometric indices, fasting glucose, insulin, HbA1c, adiponectin, leptin, hs-CRP, and TNF-α were measured. Insulin resistance was defined as HOMA-IR ≥3.0. Statistical analyses included independent t-tests, Mann-Whitney U tests, Spearman correlations, and multiple logistic regression. **Results:** The overweight/obese group had significantly higher median HOMA-IR (4.32 vs. 1.85; p<0.001), with 72.8% of the overweight/obese group meeting criteria for insulin resistance, versus 15.0% of controls. The obese had significant endocrine abnormalities, lower adiponectin (4.8 vs. 11.2 µg/mL, p<0.001) and higher leptin (28.4 vs. 6.8 ng/mL, p<0.001) levels, as well as higher levels of inflammatory markers (hs-CRP: 3.8 vs. 1.1 mg/L, p<0.001 and TNF-α: 8.9 vs. 4.2 pg/mL, p<0.001). Waist-to-Height Ratio (WHtR) was the most strongly correlated with HOMA-IR (r=0.74, p<0.001). In multiple logistic regression, WHtR ≥0.5 (AOR: 4.85), family history of T2DM (AOR: 2.34), leptin/adiponectin ratio (AOR: 1.42 per unit) and hs-CRP >3.0 mg/L (AOR: 2.15) were found to be independent predictors of insulin resistance. **Conclusions**: Pediatric obesity in Islamabad is associated with a significant imbalance of adipokines and systemic inflammation levels which are associated with high insulin resistance. WHtR is a better and low-cost screening tool for metabolic risk in this population. Anthropometric and biomarker evaluation is essential for early detection of endocrine dysfunction and to avoid progression to youth onset T2DM in urban children of Pakistan.

KEYWORDS: Pediatric obesity, insulin resistance, adipokines, type 2 diabetes, waist-to-height ratio, Islamabad, Pakistan, endocrine mechanisms.

INTRODUCTION:

The escalating global prevalence of pediatric obesity represents one of the most critical public health challenges of the 21st century. Over the past three decades, the incidence of obesity in children and adolescents has risen at an alarming rate[1], driven by obesogenic environments characterized by high-calorie dietary patterns and increasingly sedentary lifestyles [2]. This epidemic is no longer confined to high-income nations; it has become a pervasive global crisis, disproportionately affecting vulnerable populations and placing an unprecedented burden on healthcare systems worldwide [3]. While the consequences of childhood obesity for immediate health are significant, it is the long-term metabolic consequences that threaten future generations [4]. Type 2 diabetes mellitus (T2DM) was once thought of as a disease of middle age and older, but now more frequently is being diagnosed in the pediatric and adolescent population [5]. This epidemiological change is closely related to the increasing prevalence of severe childhood obesity [6]. Pediatric T2DM is a complex metabolic disorder, unlike type 1 diabetes that is primarily an autoimmune disease, and is caused by environmental and genetic factors [7]. The early presentation of T2DM in young people is especially worrying as it is linked to a more aggressive disease phenotype, rapid beta-cell dysfunction, and early development

of severe microvascular and macrovascular complications at a time when the patient is in their most productive life years [8].

The central mechanism of this metabolic degradation is insulin resistance, which is a pathological condition of decreased sensitivity of target tissues, mainly skeletal muscle, liver and adipose tissue, to normal levels of insulin in the circulation [9]. Insulin resistance is the most important pathophysiological link between excessive adiposity and the development of T2DM in the context of pediatric obesity [10]. Initially the pancreatic beta cells try to compensate by producing more insulin, resulting in hyperinsulinemia to maintain euglycemia [11]. This compensatory mechanism, however, is not unlimited and when it fails, it is the beginning of the passage from normal glucose tolerance to prediabetes and finally overt childhood diabetes [12].

In recent decades, the perception of adipose tissue has changed dramatically from being a passive energy store to a very active endocrine organ [13]. Obesity is associated with a change in the secretory profile of the hypertrophic and hyperplastic adipocytes, which release a large number of bioactive molecules, referred to as adipokines [14]. These endocrine factors are important in controlling energy homeostasis, lipid metabolism and systemic insulin sensitivity [15]. This endocrine role of adipose tissue is dysregulated in obese children and is a major contributor to the systemic metabolic abnormalities seen in obese children [16].

Among the myriad of endocrine factors secreted by adipose tissue, the imbalance between pro-inflammatory and anti-inflammatory adipokines is central to the pathogenesis of insulin resistance [17]. Adiponectin, an insulin-sensitizing adipokine, is notably suppressed in obesity, while leptin, resistin, and various pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are markedly elevated [18]. This altered endocrine milieu induces chronic, low-grade systemic inflammation, which interferes with intracellular insulin signaling cascades, particularly the insulin receptor substrate (IRS) and phosphoinositide 3-kinase (PI3K) pathways, thereby exacerbating peripheral insulin resistance [19].

The progression from compensated insulin resistance to actual childhood diabetes depends on the ability of the pancreatic beta cells to maintain hyperinsulinemia in the face of rising metabolic needs [20]. Excessive exposure to high levels of free fatty acids (lipotoxicity) and hyperglycemia (glucotoxicity) together with the negative effects of inflammatory cytokines, lead to endoplasmic reticulum stress and oxidative stress in the beta cells [21]. This leads to beta-cell apoptosis, dedifferentiation and ultimately exhaustion of the pancreas' secretory capacity which is clinically manifested by T2DM [22]. The clinical implications of this endocrine driven metabolic cascade are profound, because the developing paediatric endocrine system is uniquely vulnerable to metabolic programming [23]. Severe insulin resistance and hyperinsulinemia in early life not only hasten the onset of T2DM, but also substantially raise the lifetime risk for cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS) [24, 25]. Therefore, the exact endocrine mechanisms underlying insulin resistance in obese children and adolescents are important to determine in order to develop targeted interventions that are able to prevent or reverse insulin resistance and the development of diabetes [26].

Hence, this paper is designed to review thoroughly the endocrine mechanism of the relationship between pediatric obesity and insulin resistance and its association with childhood diabetes. This review will focus on the complex pathophysiology of pediatric T2DM, including the changes in adipokine levels, the inflammatory mechanisms that impair insulin signaling, and the mechanisms of beta-cell failure. Additionally, it will highlight some of the new biomarkers and therapeutic targets that will serve as a stepping stone for future research and clinical strategies to combat the devastating effects of childhood diabetes [27].

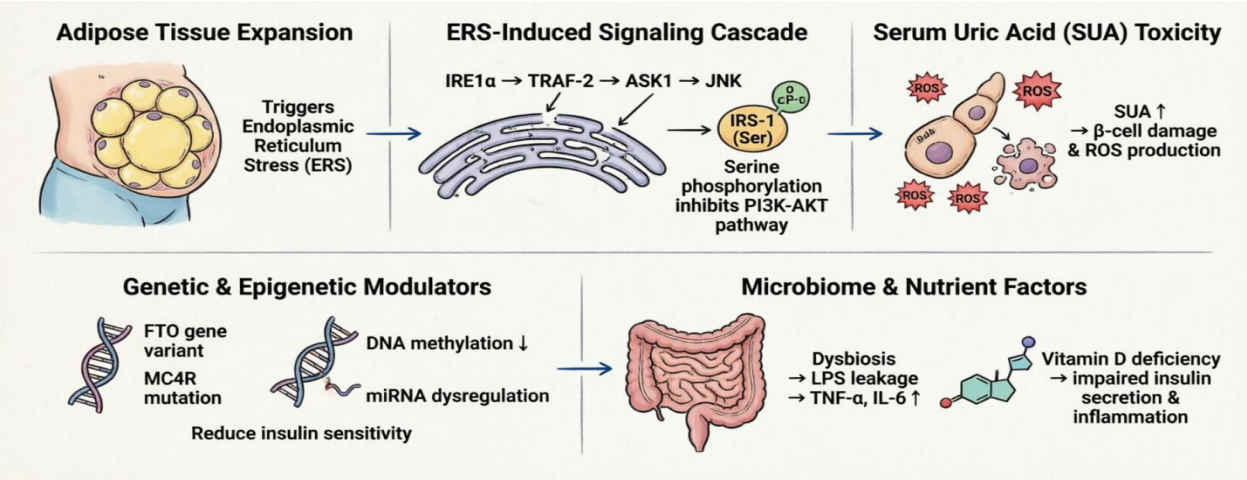


Figure: 01 Endocrine Mechanisms linking Pediatric Obesity to Insulin Resistance & type 2 Diabetes

This diagram shows the complicated and interwoven biological pathways that contribute to insulin resistance and type 2 diabetes as a result of physiological stress, genetics and environment. In the primary pathway (top row), obesity leads to Endoplasmic Reticulum Stress (ERS) which initiates a cellular signaling pathway that eventually inhibits the insulin-sensitizing PI3K-AKT pathway, while high levels of Serum Uric Acid (SUA) cause toxic oxidative stress (ROS) that damages the insulin-producing beta cells of the pancreas. Genetic and epigenetic factors (such as FTO gene variants and altered DNA methylation) that intrinsically lower insulin sensitivity, as well as environmental factors (such as gut microbiome dysbiosis that leads to release of inflammatory toxins and Vitamin D deficiencies that further blunt insulin secretion and promote inflammation) underlie and drive these physical processes.

LITERATURE REVIEW

Adipose tissue as an endocrine organ has revolutionized the way metabolic consequences of obesity are viewed, especially in children. Pediatric obesity is characterized by adipokine dysregulation as a result of the expansion of adipose tissue, especially visceral adipose tissue. Adiponectin/leptin ratio has been shown to be a very sensitive measure of insulin resistance in obese children, in recent studies [28]. The mechanism of action of the insulin-sensitizing effect of adiponectin involves the activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPAR-α) pathways in the liver and skeletal muscle [29]. Hyperleptinemia, on the other hand, which usually accompanies leptin resistance in obese youth, does not suppress appetite and is associated with sympathetic nervous system activation and systemic inflammation [30].

Inflammatory Pathways and Insulin Resistance:

Local and systemic inflammation plays a significant role in endocrine disruption in obesity. Increased adipocytes size induces the secretion of chemokines, including MCP-1, which attract macrophages to the adipose tissue [31]. This infiltration changes the immune profile of the adipose tissue from anti-inflammatory M2 macrophages to pro-inflammatory M1 macrophages, generating a local inflammatory microenvironment [32]. These macrophages and adipocytes produce large amounts of TNF-α and IL-6, which trigger activation of serine kinase pathways such as c-Jun N-terminal kinase (JNK) and inhibitor of kappa kinase beta (IKKβ). These kinases cause the serine phosphorylation of insulin receptor substrate-1 (IRS-1) and thus block insulin signaling and promote peripheral insulin resistance [33]. High-sensitivity C-reactive protein (hs-CRP) and IL-6 have been recently found to be closely associated with the extent of insulin resistance, independent of total body fat percentage in pediatric cohort studies [34].

Progression to Beta-Cell Dysfunction and Childhood:

T2DM While insulin resistance is the primary defect, the progression to T2DM is strictly dependent on beta-cell failure. The endocrine and metabolic stress imposed by obesity forces pancreatic beta cells to undergo significant functional adaptation. Initially, beta cells increase their mass and insulin secretory capacity. However, chronic exposure to elevated free fatty acids and glucose leads to lipotoxicity and glucotoxicity [35]. In the pediatric population, beta-cell compensation is often insufficient relative to the degree of insulin resistance, a phenomenon that distinguishes youth-onset T2DM from adult-onset T2DM [36]. Furthermore, the deposition of islet amyloid polypeptide (IAPP) and the induction of endoplasmic reticulum (ER) stress trigger apoptotic pathways within the beta cells [37]. Longitudinal studies utilizing hyperglycemic clamps in adolescents have shown a rapid and precipitous decline in beta-cell function over a short period following the diagnosis of prediabetes, highlighting the aggressive nature of the disease in youth [38].

Genetic and Epigenetic Modifiers of the Endocrine:

Milieu The endocrine mechanisms driving insulin resistance are further modulated by genetic and epigenetic factors. Genome-wide association studies (GWAS) have identified multiple loci associated with both pediatric obesity and beta-cell dysfunction, such as variants in the *TCF7L2* and *FTO* genes [39]. Moreover, the intrauterine environment plays a critical role; maternal obesity and gestational diabetes mellitus (GDM) induce epigenetic modifications in the offspring, altering the expression of genes involved in adipogenesis and insulin signaling [40]. These epigenetic changes predispose the child to a more severe endocrine dysregulation and a higher risk of early-onset insulin resistance, demonstrating a transgenerational cycle of metabolic disease [41].

Emerging Therapeutic Targets and Biomarkers:

Understanding the endocrine pathophysiology of pediatric insulin resistance has paved the way for novel therapeutic interventions. While lifestyle modification remains the cornerstone of treatment, the increasing severity of youth-onset T2DM has necessitated pharmacological interventions. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as liraglutide and semaglutide, have shown significant efficacy in improving insulin sensitivity, promoting weight loss, and preserving beta-cell function in obese adolescents [42]. These agents not only enhance glucose-dependent insulin secretion but also exert direct endocrine effects on the hypothalamus to reduce appetite and improve systemic metabolic profiles [43]. Future research must focus on identifying early endocrine biomarkers to stratify risk and personalize therapeutic approaches before irreversible beta-cell damage occurs [44].

METHODOLOGY

Study Design and Setting:

A cross-sectional analytical study was conducted between January 2024 and December 2025 at two major tertiary care centers in Islamabad, Pakistan: the Pakistan Institute of Medical Sciences (PIMS) and Shifa International Hospital. The study was designed to evaluate the endocrine mechanisms linking pediatric obesity to insulin resistance and to assess the risk of early-onset type 2 diabetes mellitus (T2DM) in the urban pediatric population of the Islamabad Capital Territory (ICT).

Study Population and Sampling The study enrolled children and adolescents aged 8 to 16 years. Participants were stratified into two groups based on World Health Organization (WHO) growth reference standards for school-aged children and adolescents:

- **Group 1 (Case Group):** Overweight and obese participants (BMI-for-age ≥85th percentile).
- **Group 2 (Control Group):** Normal-weight participants (BMI-for-age between 5th and 84th percentiles).

Inclusion Criteria: Residents of Islamabad/Rawalpindi for at least 2 years, pre-pubertal or early-pubertal (Tanner stages I–II) to minimize hormonal confounding, and parental consent with child assent. *Exclusion Criteria:* Known diagnosis of Type 1 diabetes, syndromic obesity (e.g., Prader-Willi), secondary causes of obesity (e.g., hypothyroidism, Cushing's syndrome), chronic systemic illnesses, or use of medications affecting glucose metabolism or weight (e.g., corticosteroids, atypical antipsychotics).

Sample Size Calculation:

The sample size was calculated using the WHO sample size calculator. With a 95% confidence interval, 5% margin of error and design effect of 1.5, the minimum sample size was calculated to be 342, assuming a prevalence of insulin resistance (HOMA-IR ≥3.0) of 38% among obese Pakistani children based on previous studies conducted in the region. The target sample size was determined to be N=400 (200 obese/overweight and 200 normal weight control) with a 15% non-response or attrition rate. **Data Collection and Anthropometric Measurements** Trained pediatric researchers collected data using a standardized, pre-tested questionnaire covering demographic details, family history of T2DM, dietary patterns (frequency of sugar-sweetened beverages and fast food), and physical activity levels (adapted from the International Physical Activity Questionnaire for adolescents). Anthropometric measurements were taken with participants in light clothing and barefoot:

- **Weight:** Measured to the nearest 0.1 kg using a calibrated digital scale.
- **Height:** Measured to the nearest 0.1 cm using a stadiometer.
- **Waist Circumference (WC):** Measured at the midpoint between the lowest rib and the iliac crest.
- **Waist-to-Height Ratio (WHtR):** Calculated as WC (cm) / Height (cm). A WHtR ≥0.5 was considered indicative of central adiposity.

Biochemical and Endocrine Assays After a 10- to 12-hour overnight fast, 5 mL of venous blood was drawn. Samples were centrifuged at 3000 rpm for 10 minutes, and serum was aliquoted and stored at -80°C until analysis.

- **Metabolic Panel:** Fasting blood glucose (FBG) was measured via the hexokinase method. Fasting insulin was quantified using a chemiluminescent immunoassay (CLIA). HbA1c was measured using high-performance liquid chromatography (HPLC).
- **Insulin Resistance Index:** Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated as: [Fasting Insulin (U/mL) times Fasting Glucose (mmol/L)] / 22.5. A HOMA-IR ≥3.0 was used as the cutoff for insulin resistance, consistent with South Asian pediatric thresholds.
- **Endocrine and Inflammatory Biomarkers:** Serum adiponectin, leptin, high-sensitivity C-reactive protein (hs-CRP), and tumor necrosis factor-alpha (TNF-α) were measured using commercially available, highly sensitive enzyme-linked immunosorbent assay (ELISA) kits.

Statistical Analysis:

IBM SPSS Statistics (Version 28.0) was used for data analysis. Normality of continuous variables was assessed by Shapiro-Wilk test. Data were normally distributed and presented as mean ±standard deviation (SD) and compared by independent Student's t tests. Data that were not normally distributed were reported as median and interquartile range (IQR) and analyzed by Mann-Whitney U test. Categorical data were presented in frequencies and percentages and compared by Chi-square (χ^2) test. Pearson or Spearman correlation coefficients were used to assess relationships between anthropometric indices and endocrine biomarkers. Multiple logistic regression analysis was used to determine independent factors associated with insulin resistance (HOMA-IR ≥3.0) after adjustment for age, sex and family history of diabetes. A p-value <0.05was considered statistically significant.

RESULTS

A total of 400 participants were enrolled, with 382 completing all clinical and biochemical assessments (response rate: 95.5%). The final cohort consisted of 195 children in the overweight/obese group and 187 in the normal-weight control group.

Table 1: Baseline Demographic and Anthropometric Characteristics

Variable	Overweight/Obese Group ($n = 195$)	Normal-Weight Control ($n = 187$)	p-value
Age (years), mean ±SD	11.8 ±2.4	11.5 ±2.6	0.241
Male Sex, n(%)	102 (52.3%)	98 (52.4%)	0.985
Family History of T2DM, n(%)	89 (45.6%)	41 (21.9%)	0.001*
Weight (kg), mean ±SD	58.4 ±12.1	36.2 ±8.4	0.001*
Height (cm), mean ±SD	148.5 ±11.2	146.8 ±10.9	0.132
BMI (kg/m), mean ±SD	26.4 ±3.8	16.7 ±2.1	0.001*
BMI-for-age Percentile, median (IQR)	94.2 (89.5 – 97.1)	52.0 (41.3 – 65.4)	0.001*
Waist Circumference (cm), mean ±SD	82.5 ±9.4	61.3 ±6.8	0.001*
Waist-to-Height Ratio (WHtR), mean ±SD	0.56 ±0.05	0.42 ±0.04	0.001*

Note: statistical significance ($p < 0.05$). T2DM = Type 2 Diabetes Mellitus.

The table shows the baseline characteristics of overweight/obese children (n=195) and normal weight controls (n=187) and shows that both groups have similar age (11.5-11.8 years) and sex distribution. The key findings show that the overweight/obese group had a significantly higher family history of type 2 diabetes (45.6% vs. 21.9%, p<0.001) and, as expected, significantly higher anthropometric measurements including weight (58.4 vs. 36.2 kg), BMI (26.4 vs. 16.7 kg/m²), BMI-for-age percentile (94.2 vs. 52.0), waist circumference (82.5 vs. 61.3 cm), and waist-to-height ratio (0.56 vs. 0.42), all with p<0.001. There were no differences in height between the groups, suggesting that the differences in weight and BMI were not due to differences in linear growth.

Biochemical and Endocrine

Table 2: Biochemical and Endocrine Biomarker Profiles

Biomarker	Overweight/Obese Group ($n = 195$)	Normal-Weight Control ($n = 187$)	p-value
Fasting Glucose (mg/dL), mean ±SD	94.2 ±11.5	86.4 ±7.2	< 0.001*
Fasting Insulin (U/mL), median (IQR)	18.5 (14.2 – 24.1)	8.4 (6.1 – 10.5)	< 0.001*
HOMA-IR, median (IQR)	4.32 (3.15 – 5.88)	1.85 (1.32 – 2.41)	< 0.001*
HOMA-IR ≥3.0, n(%)	142 (72.8%)	28 (15.0%)	< 0.001*
HbA1c (%), mean ±SD	5.6 ±0.4	5.1 ±0.3	< 0.001*
Adiponectin (g/mL), median (IQR)	4.8 (3.2 – 6.5)	11.2 (8.9 – 14.1)	< 0.001*
Leptin (ng/mL), median (IQR)	28.4 (21.5 – 38.2)	6.8 (4.5 – 9.2)	< 0.001*
Leptin/Adiponectin Ratio, median (IQR)	5.9 (4.1 – 8.2)	0.6 (0.4 – 0.9)	< 0.001*
hs-CRP (mg/L), median (IQR)	3.8 (2.5 – 5.4)	1.1 (0.7 – 1.6)	< 0.001*
TNF-α (pg/mL), mean ±SD	8.9 ±2.4	4.2 ±1.3	< 0.001*

Note: statistical significance ($p < 0.05$). HOMA-IR = Homeostatic Model Assessment for Insulin Resistance.

Table 2 shows that there are significant differences in metabolic and inflammatory parameters between overweight/obese and normal weight subjects; all differences are highly statistically significant (p<0.001). Insulin resistance was clearly evident in the obese group with significantly higher fasting glucose, insulin, HbA1c and HOMA-IR (72.8% were ≥3.0 compared with 15.0% of controls). Moreover, they presented a very unfavourable adipokine profile with extremely low levels of protective adiponectin, high leptin levels and a significantly higher leptin/adiponectin ratio. These findings, along with significant increases in inflammatory markers (hs-CRP and TNF-α), highlight the strong biological association between excess weight, metabolic dysfunction and chronic systemic inflammation**.**

Correlation Matrix

Table 3: Correlation Matrix of Anthropometric Indices with HOMA-IR and Endocrine Markers (Entire Cohort, $N = 382$**)**

Variable	HOMA-IR (r)	Adiponectin (r)	Leptin (r)	hs-CRP (r)
BMI (kg/m)	0.68*	-0.54*	0.72*	0.61*

Waist Circumference (cm)	0.71*	-0.58*	0.75*	0.65*
Waist-to-Height Ratio (WHtR)	0.74*	-0.61*	0.78*	0.69*
Fasting Insulin (U/mL)	0.89*	-0.42*	0.65*	0.51*

Table 3, anthropometric measures and metabolic markers were highly correlated in all 382 participants and these correlations were statistically significant. Waist-to-Height Ratio (WHtR) had the highest correlation with HOMA-IR (r=0.74), leptin (r=0.78) and hs-CRP (r=0.69) and might be the most sensitive measure of metabolic dysfunction. All anthropometric indices were positively associated with insulin resistance and markers of inflammation and inversely associated with protective adiponectin (r=-0.54 to -0.61). The strong correlation between fasting insulin and HOMA-IR (r=0.89) underscores their close association, and the strong relationships among the central obesity measures and adverse biomarkers further emphasize the importance of fat distribution in metabolic health.

Multiple Logistic Regression Analysis:

Table 4: Multiple Logistic Regression Analysis for Predictors of Insulin Resistance (HOMA-IR ≥3.0)

Predictor Variable	Adjusted Odds Ratio (AOR)	95% Confidence Interval (CI)	p-value
WHtR ≥0.5	4.85	2.91 – 8.08	$< 0.001^*$
Family History of T2DM	2.34	1.45 – 3.78	$< 0.001^*$
Leptin/Adiponectin Ratio (per 1-unit increase)	1.42	1.28 – 1.57	$< 0.001^*$
hs-CRP > 3.0mg/L	2.15	1.32 – 3.51	0.002*
Sedentary Lifestyle (> 4 hrs/day screen time)	1.68	1.05 – 2.69	0.031*
Age (per year increase)	1.12	0.98 – 1.28	0.095
Male Sex	0.94	0.61 – 1.45	0.782

Note: Model adjusted for age, sex, and BMI. statistical significance ($p < 0.05$).

Table 4 shows the independent predictors of insulin resistance (HOMA-IR ≥3.0) with central obesity being the most powerful predictor, as the Waist-to-Height Ratio (WHtR) ≥0.5 was associated with almost 5 times the odds of insulin resistance (AOR 4.85). Other important independent predictors are a family history of Type 2 Diabetes, high systemic inflammation (hs-CRP >3.0 mg/L), high leptin/adiponectin ratio and sedentary lifestyle. In contrast, age and sex were not statistically significant predictors when adjusted for these metabolic and lifestyle factors, suggesting that fat distribution, genetics, inflammation and lifestyle are the main contributors to insulin resistance in this group.

Summary:

This study conducted in Islamabad reveals a profound endocrine imbalance in children with overweight and obesity. The prevalence of insulin resistance was significantly higher in the overweight/obese group as compared to the non-overweight/obese group (72.8% vs. 15.0%, p<0.001). The pathophysiological link was clearly demonstrated by the changes in the adipokine profile, which included a very strong decrease of insulin-sensitizing adiponectin and a strong increase in leptin, hs-CRP, and TNF-α. Interestingly, the Waist-to-Height Ratio (WHtR) was found to be the best anthropometric predictor of insulin resistance (r=0.74, p<0.001), as compared to BMI alone. Multiple logistic regression analysis showed that central adiposity (WHtR ≥0.5), high ratio of leptin to adiponectin, systemic inflammation (hs-CRP >3.0) and family history of T2DM were independent and strong predictors of insulin resistance in paediatric population of urban Pakistan. These findings highlight the need for early screening in Paediatric clinics of Islamabad through simple anthropometric measures (such as WHtR) and life style interventions to reduce the looming threat of childhood T2DM.

CONCLUSION:

These findings among children in Islamabad highlight the importance of understanding that obesity in children is not just a state of being overweight but a serious endocrine disorder with extreme insulin resistance and systemic inflammation. Results further substantiate that overweight and obese children in this urban population have a unique pathological profile, characterized by significantly higher HOMA-IR and lower adiponectin levels and significantly higher levels of leptin, hs-CRP, and TNF-α. It is these endocrine changes that provide the main mechanistic link between excess adiposity and early metabolic dysfunction and the subsequent development of type 2 diabetes mellitus (T2DM). One of the key findings of this research is that the Waist to Height Ratio (WHtR) is more predictive than traditional Body Mass Index (BMI) of children at high risk of insulin resistance. The WHtR ≥0.5 emerged as the

strongest independent predictor of metabolic compromise (aOR: 4.85), providing a simple, non-invasive anthropometric measure that can be used as an effective and cost-efficient tool for early screening in resource-constrained primary care settings throughout Pakistan. Moreover, the strong relationship between positive family history of T2DM and insulin resistance suggests a synergic effect of genetic susceptibility and obesogenic environmental factors in the local population.

The significant imbalance of leptin to adiponectin, coupled with the fact that there is chronic low grade inflammation, is a sign of the urgent need to intervene before beta cell damage becomes irreversible. The aggressive phenotype of youth-onset T2DM reported in literature around the world and high prevalence of insulin resistance (IR) (72.8%) in the obese group indicates impending public health crisis in Islamabad. Hence, clinical protocols need to be changed from reactive management of overt diabetes to proactive management of prediabetic state by routine evaluation of central adiposity and inflammatory biomarkers. To sum up, Pakistan should adopt a comprehensive strategy to reduce the burden of childhood diabetes by combining early endocrine screening with lifestyle interventions. Public health programs should focus on decreasing sedentary time and enhancing dietary habits, especially in families with a history of T2DM. Longitudinal studies are needed in future to follow-up this group and assess the long-term effectiveness of early use of pharmacological interventions including GLP-1 receptor agonists to maintain beta-cell function in high-risk Pakistani adolescents who are progressing from insulin resistance to T2DM. Healthcare providers can break the cycle of transgenerational metabolic disease and enhance the long-term health of the nation's children by addressing the endocrine causes of pediatric obesity.

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