# Fasting Plasma Glucose and Clustering of Cardiometabolic Risk Factors in Normoglycemic Outpatient Children and Adolescents

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**OBJECTIVE**—To evaluate whether fasting plasma glucose (FPG) within a normoglycemic range is associated with cardiometabolic risk factors (CMRF) among children and adolescents in an outpatient setting.

**RESEARCH DESIGN AND METHODS**—Subjects (780; age 6–16 years) with FPG <100 mg/dL were divided into tertiles of FPG.

**RESULTS**—BMI, waist circumference, homeostasis model assessment-insulin resistance, systolic blood pressure, and white blood cell (WBC) count ($P < 0.0001$) increased across tertiles of FPG. Subjects with high-normal FPG (89–99 mg/dL) showed a higher risk of insulin resistance, hypertension, and high WBC count compared with subjects with low-normal FPG, independent of BMI *z* score.

**CONCLUSIONS**—In outpatient children and adolescents, higher FPG within the normal range is associated with several CMRF, independent of obesity. Thus the simple measurement of FPG may help identify subjects who warrant some monitoring in relation to cardiovascular risk.

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The prevalence of prediabetes, defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), is increasing in the pediatric population (1). Similar to adults, prediabetes in children is associated with both an elevated risk of developing type 2 diabetes and a worsened cardiovascular risk profile compared with normoglycemic subjects (2,3). Recent studies have shown that in obese children some impairment of glucose homeostasis might already be present at fasting glucose concentrations below the threshold for IFG (4–6). However, the question whether fasting plasma glucose (FPG) in the normal range is associated with some cardiometabolic risk factors (CMRF) is little explored. Therefore, we assessed whether FPG clustered with CMRF in an outpatient setting of normoglycemic Caucasian children and adolescents. In addition we evaluated whether subjects with high-normal FPG showed a worse cardiometabolic risk profile.

## RESEARCH DESIGN AND METHODS

Our population consisted of 780 Southern European Caucasian children and adolescents (age 6–16 years) consecutively observed in the Outpatient Unit of Pozzuoli Hospital in the period 2004–2009. One hundred ninety-eight (25%) were normal weight, 174 (22%) were overweight, and 408 (52%) were obese. All subjects had been referred to our unit by their general practitioners because of allergy problems, overweight, or obesity. None were under pharmacological treatment. Subjects with IFG; diabetes; and gastrointestinal, cardiac, renal, urinary, and infectious diseases were excluded. Anthropometric measurements and blood pressure (BP) were obtained with standard methods as elsewhere described (7). Biochemical and hematological variables were centrally analyzed according to standard procedures. Insulin sensitivity was evaluated by the homeostasis model assessment-insulin resistance (HOMA-IR). Overweight and obesity were defined using Italian growth charts, according to individual BMI ≥85th and ≥95th percentile for age and sex, respectively (8). Hypertension was defined by BP ≥95th percentile for age, sex, and height as elsewhere reported (9). IR was defined by 95th percentile of HOMA-IR values obtained in healthy nonobese Italian children categorized according to Tanner stage (10). High white blood cell (WBC) count was defined by a value ≥9.0 ($10^3$/L) corresponding to the 80th percentile of our population. The local ethics committee approved the study, and informed consent was obtained from all children's parents. Data were analyzed by ANOVA, $\chi^2$, and multiple logistic regression analysis using SPSS for Windows, version 13.0 (SPSS, Chicago, IL).

## RESULTS

Table 1 shows the features of subjects according to tertiles of FPG: low-normal (≤82 mg/dL), mid-normal (83–88 mg/dL), and high-normal (89–99 mg/dL). Age and Tanner stage were similar among the three categories of FPG. The percentage of male sex and obesity increased across categories of FPG ($P < 0.001$). From the lowest to the highest tertile of FPG, we observed a significant increase in BMI, waist circumference, HOMA-IR, systolic BP, and WBC count ($P < 0.0001$). No difference was observed for $HbA_{1c}$ and lipid profile. At multiple logistic regression analysis (controlled for age, sex, Tanner stage, allergy, and BMI *z* score), subjects with high-normal

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**Table 1—*Anthropometric, clinical, and biochemical variables among categories of FPG and risk of CMRF in children and adolescents***

| | Normal | | | |
|---|---|---|---|---|
| Categories of FPG | Low | Mid | High | *P* |
| *n* | 274 | 275 | 231 | |
| Age (years) | 10 ± 3 | 10 ± 3 | 10 ± 3 | 0.101 |
| Boys (%) | 110 (40) | 143 (52) | 129 (56) | 0.001 |
| Prepubertal stage (%) | 135 (49) | 145 (53) | 112 (49) | 0.586 |
| Normal weight (%) | 92 (33) | 61 (22) | 45 (20) | 0.0001 |
| Overweight (%) | 62 (23) | 59 (21) | 53 (23) | 0.554 |
| Obesity (%) | 120 (44) | 155 (56) | 133 (58) | 0.001 |
| BMI (kg/m$^2$) | 24 ± 6 | 25 ± 6 | 26 ± 6 | 0.0001 |
| BMI *z* score | −0.22 ± 1.0 | 0.02 ± 0.96 | 0.19 ± 1.02 | 0.0001 |
| Waist circumference (cm) | 77 ± 17 | 82 ± 16 | 85 ± 17 | 0.0001 |
| HOMA-IR | 1.9 ± 1.4 | 2.7 ± 2.1 | 3.4 ± 2.5 | 0.0001 |
| $HbA_{1c}$ (%) | 5.4 ± 0.3 | 5.4 ± 0.3 | 5.3 ± 0.3 | 0.118 |
| Cholesterol (mg/dL) | 162 ± 33 | 163 ± 30 | 161 ± 32 | 0.792 |
| HDL cholesterol (mg/dL) | 52 ± 11 | 53 ± 11 | 52 ± 12 | 0.264 |
| Triglycerides (mg/dL) | 84 ± 40 | 87 ± 44 | 84 ± 36 | 0.902 |
| BP (mmHg) | | | | |
| Systolic | 103 ± 11 | 107 ± 12 | 110 ± 13 | 0.0001 |
| Diastolic | 60 ± 9 | 60 ± 10 | 61 ± 9 | 0.542 |
| WBC (10$^3$/L) | 7.1 ± 2.4 | 7.4 ± 2.0 | 7.9 ± 2.3 | 0.0001 |
| Odds ratio (95% CI)^ | | | | |
| Insulin resistance | 1.00 | 2.35 (1.43–3.87)* | 1.95 (1.52–2.51)† | |
| Hypertension | 1.00 | 2.23 (1.06–3.08)‡ | 1.57 (1.07–2.29)§ | |
| High WBC count | 1.00 | 1.00 (0.63–1.58) | 1.31 (1.05–1.65)§ | |

Data are mean ± SD or *n* (%) unless otherwise indicated. ^Adjusted for age, sex, pubertal stage, allergy, and BMI *z* score; *$P < 0.001$; †$P < 0.0001$; ‡$P < 0.05$; §$P < 0.025$.

FPG showed an increased risk of IR, hypertension, and high WBC count compared with subjects with low-normal FPG (Table 1). The group with mid-normal FPG, as compared with the low-normal FPG, showed an increased risk of IR and hypertension, but not of high WBC count. These results did not change when the category of overweight/obesity was included into the model instead of BMI *z* score.

**CONCLUSIONS**—This study demonstrates that in an outpatient setting of normoglycemic Caucasian children and adolescents, FPG is associated with several CMRF, independent of obesity. In adults, a high but normal FPG is a risk factor for development of type 2 diabetes (11) and cardiovascular disease (12). Previous studies exploring the clinical significance of high-normal FPG in children have been performed in obese subjects (4–6). In a sample of 323 obese children, Grandone et al. (5) showed that high-normal FPG (87–99 mg/dL) is associated with a sevenfold higher risk of presenting IGT and IR. More recently, O'Malley et al. (6) reported a reduction in both insulin sensitivity and β-cell function at increasing FPG in normoglycemic multiethnic obese youth, thus demonstrating that some deterioration of glucose homeostasis is already present at apparently normal FPG. Our study extends this observation by demonstrating that FPG is associated with a cluster of CMRF and demonstrates that this relation is independent of BMI. Actually, subjects with FPG between 89 and 99 mg/dL not only present IR but also show a 60% increased risk of hypertension and a 30% increased risk of high WBC count than those with FPG ≤82 mg/dL.

A positive association between FPG and BP has been previously demonstrated in children with IFG (2). Our study provides the novel evidence that this relation is also present at FPG within the normal range. Thus the finding of a high-normal FPG in a clinical setting could contribute to an early detection of elevated BP levels, a condition frequently underestimated in childhood (13).

An increased WBC count has been recently reported in children and adolescents with the metabolic syndrome (14). We show that this trait is detectable also in children with high-normal FPG, indicating that systemic inflammation may appear early in life and be related to subclinical abnormalities of glucose metabolism.

In conclusion, in an outpatient setting of Caucasian children and adolescents, FPG within the normal range is associated with several CMRF, independent of obesity. Subjects with high-normal FPG show a worse cardiometabolic profile than those with low-normal FPG. Although our observations need to be confirmed in the general pediatric population, the simple measurement of FPG may help in identifying children who warrant some monitoring. Longitudinal studies will confirm whether high-normal FPG in childhood could be considered a marker of cardiovascular risk and a predictor of hard outcomes in adulthood.

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