Glucose levels are not the same for everyone: A real-world big data study evaluating glucose levels by sex and age among children

Carmit Avnon Ziv (zcarmit@gmail.com)  
Shaare Zedek Medical Center  
https://orcid.org/0000-0001-8236-1974

Tamar Banon  
Maccabi Healthcare Services

Amir Ben Tov  
Tel Aviv University Sackler Faculty of Medicine

Gabriel Chodick  
Tel Aviv University Sackler Faculty of Medicine

Linoy Gabay  
Maccabi Healthcare Services

Adi Auerbach  
Shaare Zedek Medical Center

Harry J. Hirsch  
Shaare Zedek Medical Center

Floris Levy Khademi  
Shaare Zedek Medical Center

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Abstract

Purpose: Understanding the normal range of laboratory values as pertained to different age groups and males or females is paramount in health care delivery. We aimed to assess the distribution of glucose levels by age and sex in the general population of children using a large-scale population-based cohort.

Methods: A retrospective study with real-world de-identified data from a large, state mandated health fund in Israel among children aged 2 to 18 years old between 2006 and 2019. Age, sex, and BMI differences in mean glucose levels were evaluated using 3-way Anova.

Results: Study included 130,170 blood samples from 117,411 children, 53.3% were female. After adjusting for age boys had higher glucose levels than girls, with a mean of 89.21 ±8.66 mg/dL vs. 87.59 ±8.35 (p<0.001).

Compared to the 15 to 18 year-olds (88.49 mg/dl ±7.63), 2 to 5 year-olds had lower glucose levels (84.19 ±10.65, (p<0.001)), 11 to 14 year-olds had higher glucose (90.40 ±7.42 (p<0.001)) and 6 to 10 year-olds showed no difference (88.45 ±8.25). Among our cohort, 33.0% (n=42,991) had a BMI percentile record the same year as their glucose test result. There was a weak yet significant positive association between blood glucose levels and BMI (Pearson coefficient <0.1).

Conclusions: Our large cohort indicates that boys have higher glucose levels than girls, as do adolescents compared to younger children. This finding is important for the delivery of adequate health care, screening for illness and avoiding unnecessary investigations and tests.

Introduction

In the clinical setting, blood tests assist physicians in ascertaining their patients’ state of health. Understanding the normal values of different tests, as well as the differences in those values among different ages and between sexes, is paramount in delivering adequate health care, screening for illness and avoiding unnecessary investigations.

The establishment of correct reference ranges according to age and sex is complex. Earlier ranges for various biochemical markers and hormones were based on adult levels, on samples obtained from hospitalized children or small cohorts. Some values, such as alkaline phosphatase and sex hormones change with age and differ between the sexes. Knowing this allows the physician to interpret lab results accordingly.[1]

Reports of glucose levels in children date back to the beginning of the 20th century. The first studies of normal ranges for glucose levels in children were done on small cohorts of a few dozen children and did not show any differences between age groups or sex.[2] Reference studies were done in the beginning of the 21st century. Some, such as CALIPER (Canadian Laboratory Initiative in Pediatric Reference Intervals) are relatively small scale - consisting of 2,188 children, newborn to 18 years of age.[3] Some later studies with larger cohorts of about 7000 children, do suggest higher glucose in males, but do not cover children of all ages.[4, 5] These differences may be relevant, as higher glucose levels portend health concerns such as future diabetes—even within normal limits.[6]

In relationship to adiposity indexes, obese females have higher insulin resistance than their male counterparts. Associated cardiometabolic risk factors were also higher in females.[7] It has been shown that the nuclear receptor Estrogen receptor 1 improves glycemic homeostasis, whereas Estrogen receptor 2 impairs glycemic homeostasis, through their actions on muscle GLUT4. GLUT4 is an insulin sensitive glucose transporter and is an important factor of glucose clearance.[8] Higher levels of glucose during adolescence can be due to insulin resistance of puberty.[9] Thus, we may assume there is a difference in glucose levels between males and females, and among different ages, as sexual maturation ensues.

Maccabi Health Services (MHS) allows the opportunity to harvest and research copious amounts of medical data, enabling the understanding of glucose levels in large populations. The use of electronic medical records as a source for data collection studies has been a new trend for epidemiological research in recent years, enabled by advanced informatics systems. This type of data collection allows follow-up on a large scale of sizeable cohorts and over long periods of time, enabling to maximize or minimize the effects of rare occurrences. Today there are models for integrating retrospective data and upholding ethical standards.[10]

The objective of this study is to assess the distribution of glucose levels by age and sex in the general population of children, using a large-scale informatics system, in order to highlight these differences and establish the need for age and sex related indexes.

Methods

This is a retrospective study with real-world data from MHS evaluating age and sex differences in mean glucose levels among children. This study includes a 14-year comparison between 2006 and 2019.

Data
The study used de-identified data from the MHS central computerized database. MHS is the second largest state-mandated health provider in Israel, serving more than 2.5 million members (25% of the national population). This fully computerized database captures all information on patient interactions with the medical system, which includes patient demographics, medical visits, diagnoses, medication prescriptions and medication dispenses.

**Study population**

This study included boys and girls ages 2 to 18 years-old for each year of the study period (2006 to 2019) with a blood glucose test done only in outpatient clinics and not in an urgent care setting. Samples were taken from members of a heath plan that includes Jewish Ashkenazi and Sepheradic descent, Arab descent and Druze descent. With the intention of studying the normal range of glucose in apparently healthy children, patients with extremely high or low glucose values (i.e. less than 50 mg/dL and or over 140 mg/dL) were excluded from the study population. For these reasons, any patients in the MHS diabetes registry diagnosed with type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) or with diabetic medication purchase history were excluded. In addition, any patients with a chronic illness code were also excluded from the study; this ensures that children with a continuous purchase history of medications were removed (the flow of data selection is depicted in Fig. 1). Each patient's last glucose test result from each calendar year was used in this study; therefore, the population includes very few multiple samples: 130,170 samples from 117,411 children. (9.8% of the population had repeated testing, thus more than one test sample, throughout the study period. An analysis was done on the cohort with repeated glucose measurements, where very comparable results were obtained).

**Glucose testing**

Since 2001 blood samples from all MHS clinics in Israel are sent to one central laboratory.

The blood is analyzed with either a Beckman-Coulter AU5400 biochemical analyzer or a Beckman-Coulter AU5800 biochemical analyzer[11]. The methods of blood collection, reagent kits, delivery, standardization and reference values have not changed in the MHS laboratories.

Referrals for blood glucose testing include instructions for an eight hour fast. The lab technicians are instructed to inquire fasting state when arriving for blood test. All blood tests are done during morning hours.

**Variables and Statistics**

Differences in blood glucose levels between sexes and ages were explored in this study. Patients were divided into four age groups: 2 to 5 years, 6 to 10 years, 11 to 14 years and 15 to 18 years, as shown in the Caliper study.[12] The study period was also categorized into the following groups of years: 2006 to 2010, 2011 to 2015 and 2016 to 2019 (will be referred to as "test year groups" in results). Figures such as bar graphs and error bar graphs were presented with 97.5% confidence intervals (C.I.) in order to observe any overlap for comparison between groups. Student's T-tests were performed to analyze the glucose levels between male and female patients and between age groups (comparing younger groups to the eldest children, 15 to 18 years old) for each test year group. Generalized linear modeling was used to perform a three-way ANOVA analysis comparing mean glucose levels with three factors—sex, age groups, and test year groups.

A sub-analysis was performed among children who also had a body mass index (BMI) percentile result matched with the same year as their glucose test result (33% of the study population). A Pearson's correlation test was performed to analyze the association between glucose and BMI percentile among healthy children.

BMI percentile as indexed by the world health organization [13] was treated as a continuous variable for the statistical analysis, and was recoded into six categories of < 3%, 3–15%, 15–50%, 50–85%, 85–95% and > 95% for the graphical presentation of glucose vs. BMI.

**Ethics**

The study was approved by MHS ethics committee (No. MHS-20-0010).

**Results**

A total of 130,170 samples from 117,411 children aged 2–18 years were included in this study. 0.78–1.72% of the total children in MHS had a blood glucose test every year of the study. In the test year groups, 27.0% of children had a glucose test in 2006–2010, 36.8% in 2011–2015 and 36.2% in 2016–2019. The number of glucose tests had more than doubled throughout the years, starting with 6,241 children in 2006 to 12,740 children in 2019. The mean glucose for the full population was 88.34 mg/dl (± 8.53) (4.9 mmo/l (± 0.47)) .

Overall, boys had significantly higher mean glucose results compared to girls. The average for all years for boys was 89.21 (± 8.66; 2.5 and 97.5 percentiles = 73.00 and 107.00) mg/dL and girls was 87.59 (± 8.35; 2.5 and 97.5 percentiles = 72.00 and 105.00) mg/dL (Table 1; Fig. 2a). Similar significant differences between sexes were shown in all test year groups. As for age groups, comparative to the older 15–18 year old category, the 2 to 5 year olds had significantly lower glucose levels. In contrast, the 11 to 14 year olds had significantly higher glucose levels than the oldest
children. Children between the ages of 6 to 10 years old showed no statistically significant differences in blood glucose levels compared to the 15 to 18 year olds (Table 1; Fig. 2b). A linear graph for the latest test year group with mean glucose and 97.5% C.I. is shown in Fig. 3.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Number of patients, mean blood glucose results (mg/dL ± SD) per test year group for mean glucose comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16,578 (47.1)</td>
</tr>
<tr>
<td>Female</td>
<td>18,585 (52.9)</td>
</tr>
<tr>
<td>Age groups (years)</td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>5,622 (16.0)</td>
</tr>
<tr>
<td>6–10</td>
<td>10,381 (29.5)</td>
</tr>
<tr>
<td>11–14</td>
<td>9,866 (28.1)</td>
</tr>
<tr>
<td>15–18*</td>
<td>9,294 (26.4)</td>
</tr>
<tr>
<td>Total</td>
<td>35,163</td>
</tr>
<tr>
<td>*The older group, 15–18 years old, is the comparison group for t-test analyses</td>
<td></td>
</tr>
<tr>
<td>**2016–2019 is the comparison group for test year groups</td>
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</tbody>
</table>

When comparing boys to girls, age groups to the 15–18 year olds, and test year groups to 2016–2019, there were significant differences (p < 0.05) among all three factors. The ANOVA results also suggested that boys have higher glucose levels (β = 1.842). Compared to older children, the younger 2 to 5 year-olds have lower glucose levels (β=-4.524) and the 11 to 14 year-olds have higher glucose (β = 1.824). The children in the 6 to 10 year age group also showed statistically significant differences compared to the older children, however with a lower change in glucose levels (β=0.150). Among the test year groups, comparatively to the most recent years in 2016–2019, the earlier 2006 to 2010 and 2011 to 2015 categories had significantly lower glucose (β=-0.668 and β=-0.324, respectively).

A sub-analysis was done to evaluate the correlation between blood glucose levels and BMI percentile. For the entire population, 33.0% (n = 42,991) had a BMI percentile recorded in the same year as their glucose test results, and were, therefore eligible for this sub-analysis. Pearson's test for correlation suggested that although there is an increase of glucose as BMI percentile increases (Fig. 4), there is only a weak correlation between glucose and BMI percentile (Pearson coefficient 0.088. When the same test was performed with stratification by sex and by age group, results were similar (Pearson coefficient < 0.1).

**Discussion**

We found in our cohort that boys aged 2 to 18 years have higher glucose levels. Children aged 2 to 5 years have significantly lower glucose than 15 to 18 year-olds and 11 to 14 year-olds have significantly higher glucose levels. There is a low but significant association between high BMI and higher glucose levels.

For over 100 years we have been looking at glucose as a fixed range, irrelevant of sex and age. Bass, in 1915, was among the first to determine the normal range of glucose levels in 60 children and found that it does not differ much from the range in adults. Rudesill and Henderson showed in 1941 that 98% of blood glucose levels in children were between 70 and 105 mg/dl. Both studies were small-scale and did not report differences in age groups nor between sexes.[2][14] Normal fasting plasma glucose is defined today between 65–100 mg/dl (3.5–5.5 mmol/l) for all children excluding infants and is the same for both sexes.[15] The level of 109 mg/dl was chosen almost arbitrarily as the upper threshold of normal glucose in adults, because levels higher than 109 mg/dl are associated with greater risk of vascular complications and the development of diabetes—later coined “prediabetes”.[16] Population studies showed that lowering the threshold to 100 mg/dl proved a better predictor for the development of diabetes.[17]
In recent years, glucose levels in children were determined through glucose reference studies. CALIPER (Canadian Laboratory Initiative in Pediatric Reference Intervals) is a commonly referenced relatively small-scale study, which consisted of 2,188 children, newborn to 18 years of age. In this cohort, glucose did not vary by sex or age.[3] Larger cohort studies such as IDEFICS (“identification and prevention of dietary- and lifestyle-induced health effects in children and infants”) that surveyed 7,074 healthy children aged 3 to 11 years in Europe between 2007–2010, found that boys have higher glucose levels than girls, and that there is a linear rise in glucose with age.[5] Lai showed that children younger than 5 years of age have glucose levels which are 10% lower than those found in older children, and that girls have lower glucose than boys in 4,326 children aged 3 to 15 years.[18] A reference study from India comprised of 7,618 school children, ages 11 to 18 years, found that boys had significantly higher glucose levels than girls. The glucose levels were consistent among the age groups, except for 14 year-old boys whose glucose levels were lower. [4]

Our study shows a slightly higher range of glucose in children, 72–107 mg/dl, than is generally reported in the literature.[15][18] Although some studies show even higher reported ranges,[19] In the MHS cohort, boys display higher glucose levels throughout all age groups, and children in puberty have higher glucose levels. The overall results suggest that younger children have lower glucose levels. These lower glucose levels raise questions about whether the cut off for hyperglycemia should be lowered in this age group. Additionally questioning if higher levels of glucose that are considered within the norm can predict adverse health issues later on in life.

A host of factors may affect glucose homeostasis including glucose intake, insulin and glucagon secretion, and endogenous liver glucose production (gluconeogenesis). The counterregulatory hormones such as growth hormone and cortisol are increased during fasting. In the fed state glycogenolysis, lipolysis and ketogenesis are suppressed.[15] During puberty there is insulin resistance (IR) and decreased insulin sensitivity in healthy children.[9] There is a correlation between the increase in growth hormone (GH), which is known to cause IR, and insulin like growth factor 1 (IGF1).[9][20] As for the sex differences in glucose levels, insulin levels are higher in girls than in boys in these age groups, and the higher insulin levels may indicate variable degrees of insulin resistance.[4, 5] In adults, it has been shown that the estrogen receptors affect the glucose transporters and through them glucose metabolism.[8] In our study as in others, boys have higher glucose levels than girls, even though T2DM is more prevalent in teenage girls.[21] This incongruity is yet to be explained.

Approximately 30% of the cohort had BMI measurements taken the same year as their glucose levels. Our results show that there is a weak correlation between BMI and glucose, as opposed to a study done in Sweden that showed no such correlation. [22] BMI is shown to be associated with glycemia, but it is dependant on individual variability and childhood obesity is not a strict predictor of hyperglycemia.[23] Obesity is a risk factor for T2DM in boys as well as girls, with the increase in world wide obesity a contributing factor to T2DM.[24]

There is a clinically small but statistically significant increase in glucose levels over the years of our study.

In Israel about 6% of children are obese.[25] Our results indicated there was no significant increase in BMI in this population of children during the years of the study. Neither was there a proportional increase in children with glucose levels higher than 100 mg/dl.

Strengths And Limitations

Utilizing the MHS database to retrieve data from a very large cohort, during a period of 14 years, gave this research a wealth of information. Since medications and illness affect glucose levels,[26, 27] patients were excluded if they had a diagnosis of chronic illness and/or chronic medication purchase. We did not look into the specific purchase of oral contraceptives, but the use of oral contraceptives in Israel is low at this age group.[28] The major limitation of this study is that it is retrospective and includes children who had blood tests done for various unknown reasons. BMI is measured routinely in the school system in Israel, therefore not routine in MHS. There are no recommendations for routine blood testing in Israel, which raises the question – why were these children tested? Abdominal pain, growth retardation, and parental concern are a few of the causes for “routine” blood work and some of these reasons may cause bias in such a study. The fact that the amount of blood tests per patient group has doubled itself in these years raises the same questions.

It is possible that among the large number of data points some patients would be non-fasting. Although we cannot confirm that all patients followed the strict instructions for fast before blood testing, in view of the instructions given to the families and lab technicians, and the large amount of samples, the fasting plasma glucose values are considered to be mostly reliable.

Conclusions

Our large longitudinal cohort of data indicates that there is a significant difference in glucose levels between boys and girls and age groups. Glucose levels are higher in boys than in girls. Young children have lower glucose levels than older children, and adolescents have the highest glucose levels in comparison to the younger groups. In adolescents, growth and puberty might contribute to higher glucose levels. Further studies are needed to understand the biological reasoning behind these differences. When evaluating blood test results, it is important to understand how
these results fall in consideration of the child's sex and age. Knowing the difference in glucose range between age groups can facilitate physicians in clinical decisions.

We believe this study may have a bearing not only on children's health, but also on policy making for screening and nutrition. We encourage health policymakers to perform large scale prospective studies to create adjusted reference values for different ages and sex.

**Abbreviations**

BMI
body mass index  
C.I.  
confidence intervals  
GH  
growth hormone  
IGF1  
insulin like growth factor 1  
IR  
inulin resistance  
MHS  
Maccabi Healthcare Services, Israel  
T1DM  
type 1 diabetes mellitus  
T2DM  
type 2 diabetes mellitus

**Declarations**

- **Funding**: This study was funded by Maccabi Healthcare Services "Marom", a research program for physicians in Maccabi Healthcare Services, Tel Aviv, Israel.
- **Conflict of interest**: The authors have no conflict of interest. The sponsor had no role in study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the manuscript for publication.
- **Data transparency**: The data that support the findings of this study are available from the corresponding author upon reasonable request.
- **Code availability**: not applicable
- **Authors' contributions**: Carmit Avnon Ziv, Harry Hirsch, Adi Auerbach and Floris Levy Khademi contributed to the study conception and design. Material preparation, data collection and analysis were performed by Carmit Avnon Ziv, Tamar Banon, Amir Ben Tov, Linoy Gabay and Gabriel Chodick. The first draft of the manuscript was written by Carmit Avnon Ziv and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
- **Ethics approval**: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the MHS ethics committee (No. MHS-20-0010).
- **Consent to participate**: not applicable
- **Consent for publication**: not applicable

**References**

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28. E. Havron, S. Havron, (n.d.)

Figures
Figure 1 - Flowchart of patient inclusion criteria

All children with glucose tests (last one per year) between 2006-2019
n=145,557

Excluding children with extreme glucose levels below 50mg/dL or above 140mg/dL (exclusion of 973 patients)
n=144,684

Excluding children who were in the MHS diabetes registry (exclusion of 1,490 patients)
n=143,194

Excluding children who had a chronic illness code during the year of their glucose test (exclusion of 13,564 patients)
n=130,170
unique IDs = 117,411 (90.2%)
Figure 2  
a. Mean blood glucose levels for male, female, and full population per test year groups b. Mean blood glucose levels for children in four age groups per test year groups

Figure 2
a. Mean blood glucose levels for male, female, and full population per test year groups b. Mean blood glucose levels for children in four age groups per test year groups
Figure 3 - Mean glucose for males and females vs age (n= 47108) for the years 2016-2019

Mean glucose for males and females vs age (n= 47,108) for the years 2016-2019
Figure 4 - Mean glucose vs BMI Percentile per age group (n=42,991 patients)

Mean glucose vs BMI Percentile per age group (n=42,991 patients),