

Prevalence of cardiometabolic risk factors and metabolic syndrome in obese Kuwaiti adolescents

Shurooq A Boodai¹
Lynne M Cherry²
Naveed A Sattar²
John J Reilly³

¹University of Glasgow School of Medicine, Yorkhill Hospitals, Glasgow, Scotland; ²Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland; ³University of Strathclyde Physical Activity for Health Group, School of Psychological Sciences and Health, Glasgow, Scotland

Background: Childhood and adolescent obesity is associated with insulin resistance, abnormal glucose metabolism, hypertension, dyslipidemia, inflammation, liver disease, and compromised vascular function. The purpose of this pilot study was to determine the prevalence of cardiometabolic risk factor abnormalities and metabolic syndrome (MetS) in a sample of obese Kuwaiti adolescents, as prevalence data might be helpful in improving engagement with obesity treatment in future.

Methods: Eighty obese Kuwaiti adolescents (40 males) with a mean (standard deviation) age of 12.3 years (1.1 years) participated in the present study. All participants had a detailed clinical examination and anthropometry, blood pressure taken, and assessment of fasting levels of C-reactive protein, intracellular adhesion molecule, interleukin-6, fasting blood glucose, insulin, liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase), lipid profile (cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), insulin resistance by homeostasis model assessment, and adiponectin. MetS was assessed using two recognized criteria modified for use in younger individuals.

Results: The cardiometabolic risk factors with highest prevalence of abnormal values included aspartate aminotransferase (88.7% of the sample) and insulin resistance by homeostasis model assessment (67.5%), intracellular adhesion molecule (66.5%), fasting insulin (43.5%), C-reactive protein (42.5%), low-density lipoprotein cholesterol (35.0%), total cholesterol (33.5%), and systolic blood pressure (30.0%). Of all participants, 96.3% (77/80) had at least one impaired cardiometabolic risk factor as well as obesity. Prevalence of MetS was 21.3% according to the International Diabetes Federation definition and 30% using the Third Adult Treatment Panel definition.

Conclusion: The present study suggests that obese Kuwaiti adolescents have multiple cardiometabolic risk factor abnormalities. Future studies are needed to test the benefits of intervention in this high-risk group. They also suggest that prevention of obesity in children and adults should be a major public health goal in Kuwait.

Keywords: obesity, adolescents, prevalence, cardiometabolic risk factors, metabolic syndrome

Background

Childhood and adolescent obesity is associated with insulin resistance, abnormal glucose metabolism, hypertension, dyslipidemia, inflammation, liver disease, and compromised vascular function.^{1–5} As with obesity, these impairments could track into young adulthood, which increases the risk of cardiometabolic diseases and even certain types of cancer independent of adult weight.^{6,7}

Correspondence: Shurooq A Boodai
University of Glasgow School of
Medicine, Yorkhill Hospitals,
Glasgow, G3 8SJ Scotland
Email s.boodai.1@research.gla.ac.uk

The detrimental effects of adolescent obesity on subsequent risk of cardiovascular disease are partly mediated by the presence of cardiometabolic risk factors.⁸ Cardiovascular disease is the leading cause of morbidity and mortality worldwide with an estimate of 17.3 million deaths in 2008, and by 2030 this number could reach up to 23.3 million.⁹ It is widely believed that atherosclerosis begins in childhood and progresses into adulthood.^{10,11} As the number of cardiovascular disease risk factors increases in childhood, so does the severity of both coronary and aortic atherosclerosis in young adulthood.³ In the Netherlands, two-thirds of obese children and adolescents had more than one cardiovascular disease risk factor in one study.¹² In Germany and Switzerland, around 50% of obese children had at least one cardiometabolic risk factor in one study.¹³

The presence of obesity in childhood and adolescence is also related to the development of fatty liver or steatosis, which is the most common liver abnormality in this age group.¹⁴ Steatosis can be present with or without elevated liver enzymes (aminotransferases).¹⁵ For the long term, the ramifications of having persistently elevated liver enzymes and steatosis are important and could lead eventually to the development of cirrhosis.^{14,16}

In two previous studies of obese adolescents in Kuwait, we observed that their health-related quality of life was unimpaired compared with nonobese peers,¹⁷ and that their engagement with therapy to treat obesity was poor.¹⁸ It is possible that knowledge of the presence of cardiometabolic risk factors in obese adolescents may increase the engagement of adolescents and their families with efforts to treat obesity. The aim of the present study was therefore to estimate the prevalence of cardiometabolic risk factors in obese adolescents in order to provide evidence that might be useful to future obesity treatment. In the present study, we carried out assessments of obesity-related cardiometabolic risk factors that could impair vascular health and liver function. These included lipid profile (cholesterol, low-density lipoprotein [LDL], very low-density lipoprotein, high-density lipoprotein [HDL], triglycerides [TG]), interleukin-6 (IL-6), intracellular adhesion molecule (ICAM), C-reactive protein (CRP), adiponectin, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyltransferase [GGT]), and insulin resistance by homeostasis model assessment (HOMA-IR).

Materials and methods

Participants

The study was the baseline element of an intervention to treat adolescent obesity using a randomized controlled

trial, the National Adolescent Treatment Trial for Obesity (NATTO).¹⁸ We recruited 80 obese adolescents participating in the NATTO in Kuwait City¹⁸ at the preintervention stage of the trial. They were all at or above the age- and sex-adjusted 95th body mass index (BMI) percentile, which defines obesity.¹⁹ Age ranged from 10 years to 14 years. All participants underwent physical examination including anthropometric assessment (weight, height, BMI, waist circumference) and had no medical or surgical history. All participants and their parents consented to take part in the study. The study was approved by the Medical Research Committee of the Ministry of Health – Kuwait.

Blood samples were drawn for analysis for fasting blood glucose (FBG), fasting insulin, cholesterol, LDL, HDL, TG, ALT, AST, GGT, CRP, IL-6, ICAM, and adiponectin. Insulin resistance was measured by HOMA-IR (fasting insulin \times fasting glucose/22.5).²⁰

Blood pressure was measured when the participant was sitting quietly in the upright position, with the correct cuff size applied to the right arm. The reading was repeated three times, and the average of the three readings was taken.

Biochemical assessment

Cholesterol, TG, HDL, sensitive CRP, ALT, AST, and GGT assays were assessed using a C311 Roche analyzer; sensitive CRP immunotubidimetric assays with cholesterol, TG, HDL, ALT, AST, and GGT being enzymatic colorimetric. Kits were supplied by Roche Diagnosticx GmbH. IL-6, ICAM, adiponectin, and insulin analysis (enzyme-linked immunosorbent assays) was assessed using kits supplied by R&D Systems Europe Ltd (Oxford, UK) and Mercodia AB.

Cutoff points for defining the cardiometabolic risk factors and metabolic syndrome

There are two commonly used cutoff points for FBG (mmol/L), the World Health Organization (WHO) normal cutoff <6.1 mmol/L²¹ and the American Diabetes Association normal cutoff <5.6 mmol/L.²² However, in Kuwait, the official criterion used for diagnosing and classifying diabetes mellitus is the WHO criterion,²³ and so that was used in the present study.

Ideally, hyperinsulinemia is defined if insulin level exceeds the normal value according to the pubertal stage, due to the impact of physiological insulin resistance of puberty.²⁴ However, Tanner staging was not assessed during the clinical examination in the present study for social and cultural reasons. Thus, standard values of normal, borderline, and

high fasting insulin levels proposed by the American Heart Association scientific statement were chosen.²⁵

HOMA-IR is a proxy for insulin resistance and is widely used in clinical settings and research, with high reliability in determining insulin resistance.²⁰ There is still a debate about the appropriate cutoff point for HOMA-IR, with proposed values of ≥ 2.5 ,^{26,27} ≥ 1.77 ,²⁸ and > 3.16 .²⁰ Keskin et al²⁰ found that HOMA-IR was the most sensitive and most specific of three proxies for defining insulin resistance, and the cutoff point for insulin resistance diagnosis based on HOMA-IR was 3.16,²⁰ so that definition was used in the present study.

Assessment of lipid profile for the participants included fasting TG, fasting cholesterol, fasting LDL, and fasting HDL. Jolliffe and Janssen²⁹ developed age- and sex-specific percentiles for lipoproteins and cholesterol, starting from age 12 years to age 20 years. However, our participants were aged 10–14 years, and it was not possible to use these lipoprotein percentiles for the whole sample. Therefore, the reference values for these parameters were taken from the National Cholesterol Education Program, with fixed cutoff points for normal, borderline, and high values regardless of sex and age.³⁰

Liver function tests were obtained in all participants and included ALT, AST, and GGT. The upper limit for ALT and AST in adults differs between populations, and differences exist between males and females.³¹ However, in studies examining the prevalence of abnormal ALT, AST, and GGT in adolescents, the most commonly used cutoff points were > 40 U/L, > 40 U/L, and > 35 U/L, respectively.^{15,32,33} Therefore, these were the values that we used as cutoff points in our study.

Markers of inflammation were assessed in all participants, including CRP.³⁴ Generally, normal and abnormal levels of CRP were developed for the adult population,^{34,35} and some studies found that the normal range in healthy adults was from 0.08 mg/L to 6.1 mg/L.³⁶ Our study used the cutoff points set by the American Heart Association and the Centers for Disease Control and Prevention.³⁴

The inflammatory cytokine IL-6 has an age-related variability with peak physiological elevation around age 4 years and 15 years in relation to cartilage and bone development.³⁷ In the literature, precise reference ranges for IL-6 vary greatly depending on the age, weight status, and sex of the participants tested.^{37–39} In the present study, we used the reference range of the control group (healthy controls $n=37$) from a study by Makni et al⁴⁰ (> 3.9 pg/mL).

Inflammatory plasma soluble adhesion molecules (ICAM) were also measured in all of the participants.⁴¹ The literature

shows that ICAM values are age related, and when applying the cutoff point for our study we chose a study by Andrys et al⁴² to establish reference range for serum soluble adhesion molecules in healthy children and adolescents aged 6–15 years, defined by values between the fifth and 95th percentiles for each inflammatory marker. The normal cutoff range for those aged 6–10 years was 206.8–486.8 ng/mL, and for those aged 11–15 years was 184.1–355.0 ng/mL.⁴²

The anti-inflammatory adipokine adiponectin was measured in all participants in the fasting state. It is normally present in plasma concentrations of 2–20 $\mu\text{g/mL}$.⁴³ Most studies comparing adiponectin concentration in obese adolescents with its concentration in healthy controls referred to “low levels” when adiponectin concentration was < 5 $\mu\text{g/mL}$, as compared with its concentration in healthy control subjects at > 10 $\mu\text{g/mL}$.^{44–46} Therefore, in the present study, we used the same cutoff points.

Hypertension was defined as a systolic and or diastolic blood pressure ≥ 95 th percentile for age, sex, and height, measured on three separate occasions.⁴⁷ Metabolic syndrome (MetS) was defined according to the International Diabetes Federation (IDF) definition⁴⁸ and the Third Adult Treatment Panel (ATP III) definition.⁴⁹ Participants were classified as having MetS if they had a waist circumference ≥ 90 th percentile plus two or more of the following criteria according to the IDF definition: TG ≥ 1.7 mmol/L, HDL < 1.03 mmol/L, blood pressure $\geq 130/85$ mmHg, and FBG ≥ 5.6 mmol/L. Classification of MetS according to the ATP III definition was based on the presence of three or more of the following criteria: waist circumference ≥ 90 th percentile, TG ≥ 1.24 mmol/L, HDL ≤ 1.03 mmol/L, blood pressure ≥ 90 th percentile, and FBG ≥ 6.1 mmol/L.

Results

Characteristics of study participants

Table 1 shows the mean and standard deviation (SD) of all measured parameters for the participants ($n=80$). The mean age was 12.3 years (SD 1.1 years).

Prevalence of cardiometabolic risk factors

Twenty-six out of the 80 participants (32.5%) had systolic and/or diastolic blood pressure ≥ 95 th percentile for age, sex, and height. Hyperglycemia and hyperinsulinemia were present in 2.5% (two of 80) and 43.8% (35/80) of participants, respectively. Insulin resistance as defined by HOMA-IR value > 3.16 ²⁰ was found in 67.5% (54/80) of participants. Out of the 80 participants, 27.5% (22/80) had a high TG level, 33.8% (27/80) had a high total cholesterol level, 20% (16/80) had a

Table 1 Descriptive parameters of the adolescents according to sex, mean (standard deviation)

Variables	All participants (n=80)	Boys (n=40)	Girls (n=40)	Number of participants with abnormality (%)	
				Borderline	High
Age, years	12.3 (1.1)	12.4 (1.2)	12.3 (1.1)	na	na
BMI Z-score	2.2 (0.3)	2.2 (0.3)	2.2 (0.3)	na	na
Waist circumference, cm	93.3 (12.2)	96.6 (12.4)	90.0 (11.2)		
Systolic blood pressure, mmHg	122 (11)	125 (11)	119 (9)	na	24 (30.0%)
Diastolic blood pressure, mmHg	77 (8)	78 (8)	77 (7)	na	14 (17.5)
Total cholesterol, mmol/L	4.7 (0.9)	4.7 (1.0)	4.7 (0.8)	25 (31.5%)	27 (33.8%)
LDL, mmol/L	3.0 (0.8)	3.0 (0.9)	3.0 (0.7)	20 (25%)	28 (35.0%)
TG, mmol/L	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	26 (32.5%)	22 (27.5%)
HDL, mmol/L	1.1 (0.2)	1.1 (0.2)	1.1 (0.3)	60 (75%) low	16 (20.0%)
FBG, mmol/L	4.7 (0.8)	4.8 (0.9)	4.5 (0.6)	na	2 (2.5%)
Fasting insulin, μ U/L	26.7 (23.8)	26.4 (25.8)	27.0 (22.0)	21 (26.5%)	35 (43.8%)
HOMA-IR	6.0 (7.3)	6.4 (9.2)	5.5 (5.0)	na	54 (67.5%)
ALT, U/L	34.2 (23.6)	42.2 (21.3)	26.1 (23.4)	na	21 (26.3%)
AST, U/L	58.1 (19.3)	63.3 (15.6)	52.8 (21.4)	na	71 (88.8%)
GGT, U/L	27.0 (12.6)	31.4 (13.9)	22.7 (9.6)	na	14 (17.5%)
CRP, mg/L	4.2 (5.1)	5.0 (4.6)	3.5 (5.5)	31 (38.5%)	34 (42.5%)
IL-6, pg/mL	2.0 (1.8)	1.9 (1.5)	2.0 (2.1)	na	6 (7.5%)
ICAM, ng/mL	461.3 (158.5)	493.2 (158.0)	429.4 (154.6)	na	53 (66.3%)
Adiponectin, ng/mL	50.7 (25.0)	47.0 (21.5)	54.4 (27.9)	na	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; FBG, fasting blood glucose; GGT, gamma glutamyltransferase; HDL, high-density lipoprotein; HOMA-IR, insulin resistance by homeostasis model assessment; ICAM, intracellular adhesion molecule; IL-6, interleukin-6; LDL, low-density lipoprotein; na, not applicable; TG, triglycerides.

low HDL level, and 35% had a high LDL level. Liver function tests showed high ALT in 26.3% (21/80) of participants, high AST in 88.8% (71/80) of participants, and high GGT level in 17.5% (14/80) of participants. CRP level was high in 42.5% (34/80) of participants, IL-6 level was high in 7.5% (six of 80) of participants, ICAM level was high in 66.3% (53/80) of participants, and adiponectin level was normal in all participants.

Table 2 shows the results of waist circumference, TG, HDL, FBG, systolic blood pressure, and diastolic blood pressure measurements using IDF and ATP III criteria.

Table 2 Metabolic syndrome prevalence using IDF and ATP III criteria in the participants

Anthropometric and biochemical variables	Mean (standard deviation)	IDF	ATP III
Waist circumference (cm)	93.3 (12.2)	66 (82.5%)	66 (82.5%)
TG (mmol/L)	1.3 (0.5)	12 (15%)	37 (46.5%)
HDL (mmol/L)	1.1 (0.2)	26 (32.5)	26 (32.5%)
FBG (mmol/L)	4.7 (0.8)	4 (5%)	2 (2.5%)
Systolic blood pressure	122 (11)	9 (11.5%)	11 (13.5%)
Diastolic blood pressure	77 (8)		
Metabolic syndrome prevalence		17 (21.3%)	24 (30%)

Abbreviations: ATP III, Third Adult Treatment Panel; FBG, fasting blood glucose; HDL, high-density lipoprotein; IDF, International Diabetes Federation; TG, triglycerides.

Seventeen of the 80 participants (21.3%) met the diagnosis of MetS by the IDF definition and 24 of the 80 participants (30%) met the diagnosis of MetS by the ATP III definition.

Discussion

The current study is the first to estimate the prevalence of cardiometabolic risk factors and MetS in a group of obese Kuwaiti adolescents. The main finding of this study was the high prevalence of multiple cardiometabolic risk factors. Out of the 16 risk factors measured, eight were high in $\geq 30\%$ of the participants (Table 1). The cardiometabolic risk factors with the highest prevalence of abnormal values included AST (88.7% of the sample), HOMA-IR (67.5% of the sample), ICAM (66.5% of the sample), fasting insulin (43.5% of the sample), CRP (42.5% of the sample), LDL (35.0% of the sample), cholesterol (33.5% of the sample), and systolic blood pressure (30.0% of the sample); 96.3% (77/80) of participants had at least one cardiometabolic risk factor as well as obesity.

As mentioned previously, participants of this study were recruited from the baseline stage of a randomized controlled trial of an office-based treatment trial for adolescent obesity in Kuwait (NATTO). One of the findings of the NATTO was poor engagement with treatment, as evidenced by the poor attendance of families in both the intervention and control arms of the trial.¹⁸ Therefore, findings from the present study might have been useful to demonstrate to the adolescents and

their families that their obesity was a medical problem, and so possibly persuade them to engage more with treatment. Moreover, all of the measured parameters in the present study, except for adiponectin, are readily accessible by physicians working in the Ministry of Health – Kuwait in the clinical setting, so their measurement could be part of any treatment protocol for adolescent obesity in the future.

Risk factors for cardiovascular disease and type 2 diabetes mellitus have extended their roots to reach children and adolescents.^{6,7,10,50–54} In a study from Iran⁵⁵ on 5,528 adolescents aged 10–18 years assessing the relationship between multiple cardiometabolic risk factors (total cholesterol, TG, LDL, HDL, blood pressure, and FBG) with BMI, low physical activity, and an unhealthy diet, BMI had the greatest direct effect on total cholesterol, LDL, TG, FBG, and blood pressure and an inverse relationship with HDL, more than that contributed by inactivity and an unhealthy diet. Kelishadi et al⁵⁵ called for immediate interventions to tackle pediatric obesity and its associated cardiometabolic risk factors in order to prevent future risk of MetS and chronic noncommunicable diseases in Iran.

Kardas et al⁵⁶ compared the levels of cholesterol, LDL, TG, HDL, FBG, blood pressure, vitamin D, and adiponectin between obese (n=63) and nonobese (n=51) Turkish adolescents aged 10–16 years. Obesity was defined as BMI >90th percentile for an age- and sex-specific Turkish reference population. Cholesterol, LDL, TG, FBG, and blood pressure were significantly higher in the obese group compared with the nonobese group. Adiponectin, vitamin D, and HDL were significantly lower in the obese group compared with the nonobese group. Mean adiponectin value for the obese group was 3.3 (± 0.89) ng/mL and in the nonobese group the mean value was 6.0 (± 1.4) ng/mL.

In the Netherlands, inpatient children and adolescents (n=80, aged between 8 years and 19 years) diagnosed with severe obesity (defined as BMI SDS ≥ 3 or BMI SDS ≥ 2.3 with comorbidities according to the growth percentiles of the Fourth Dutch Growth Study) were evaluated for the presence of multiple cardiometabolic risk factors, namely blood pressure, fasting insulin, FBG, HOMA-IR, cholesterol, LDL, TG, HDL, and CRP,⁵⁷ as part of an inpatient treatment trial for their obesity. Data showed that 80% of the participants had at least one impaired cardiometabolic risk factor as well as severe obesity. In comparison with our study, 90% of our participants had at least one impairment with regards to the same cardiometabolic risk factors assessed.

In the present study, almost a third of the participants had MetS according to the ATP III definition.⁵⁸ In a study done in Kuwait on apparently healthy female adolescents (n=431, age

10–19 years) to assess the prevalence of MetS using the same definitions that we applied to our study, it was found that MetS was present in 9.1% by the ATP III definition and 14.8% had MetS when the IDF definition was used.⁵⁹ In Saudi Arabia, the prevalence of MetS using the IDF definition was 18% among 180 obese 9- to 12-year-olds.⁶⁰ Also using the IDF definition in Lebanese adolescents, Nasreddine et al⁶¹ found that 21.2% of the 104 obese adolescents (mean age 16 \pm 1.3 years) had MetS, 3.8% of the 78 overweight adolescents (mean age 16.4 \pm 1.4 years) had MetS, and 1.2% of the 81 healthy weight adolescents (mean age 16.8 years) had MetS. In Iran, according to the ATP III definition, MetS has been found in 3.3% of Iranian adolescents (n=450, age 15–18 years).⁶² In a sample of 321 overweight, obese, and extremely obese adolescents from Brazil (obesity defined using the Centers for Disease Control and Prevention 2000 definition,¹⁹ MetS was found in around 18% of the 10- to 16-year-old adolescents using the IDF definition.⁶³ Similarly, in the US,⁶⁴ it was found that >50% of obese children and adolescents (n=439, aged 4–20 years) had MetS according to definitions modified from ATP III and WHO.²⁴ In summary, global studies suggest that, as in the present study, MetS is relatively common among obese adolescents.

The present study had a number of strengths. Our participants were generally a fairly homogenous group of Kuwaiti adolescents living in Kuwait City and recruited from three State schools who were examined for the presence of cardiometabolic risk factors, including MetS. The use of traditional markers for cardiovascular disease (ie, lipid profile and blood pressure), multiple markers for inflammation (ie, CRP, IL-6, and ICAM), and, for the first time, adiponectin in a sample of Kuwaiti adolescents, assessment of insulin resistance as well as liver function, all add to the novelty of our study.

However, our study had a number of limitations. First, it was not possible to conduct Tanner staging, due to social/cultural and practical reasons. Second, the optimal cutoff to define abnormality for a number of the cardiometabolic risk factors is unclear, but widely used cutoffs were chosen for the present study. Third, no data on changes in cardiometabolic risk factors during obesity treatment were available. Improvements in cardiometabolic risk profile might increase engagement with obesity treatment. Nonetheless, the relatively high prevalence of abnormal values for cardiometabolic risk factors found in the present study could be a useful aid to engage more families into participating in adolescent obesity treatment in future, and might also increase the level of commitment to participation by those who do take part.

Conclusion

The present study suggests that a number of cardiometabolic risk factors and MetS are prevalent in obese Kuwaiti adolescents. This observation might provide impetus to future strategies to treat pediatric obesity and to prevent or delay the appearance of cardiovascular disease and diabetes mellitus in the future adult generation. The observation might also be used to encourage greater engagement with treatment among families.

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Disclosure

The authors report no conflicts of interest in this work.

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