ORIGINAL ARTICLE

Vitamin D and cardiometabolic risk factors in adult non-diabetic offspring of type 2 diabetic parents

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Abstract

Objective: To measure serum vitamin D levels and assess its correlation with the various components of metabolic syndrome in adult non-diabetic offsprings of type 2 diabetics.

Methods: The analytical cross-sectional study was conducted from February to December 2012 at the Department of Physiology and Cell Biology, University of Health Sciences, Lahore. Data on anthropometric and physiologic/biochemical parameters was collected. Fasting blood samples were collected and serum was analysed for fasting serum insulin, fasting blood sugar, lipid profile and vitamin D. SPSS 20 was used for statistical analysis.

Results: Of the total 88 subjects in the study, 40(45.5%) were offsprings of type 2 diabetics and 48(54.5%) were offsprings of non-diabetic parents. Vitamin D deficiency (<20ng/ml) was observed in 86 (98.5%) of the subjects and 77 (87.5%) had vitamin D levels <15ng/ml. Severe deficiency (<10ng/ml) was seen in 61 (70%) subjects. Inverse correlation was observed between vitamin D and low density lipoprotein, total cholesterol, total cholesterol/high density lipoprotein ratio, Fasting Blood Sugar and homeostasis model assessment of insulin resistance.

Conclusion: The subjects were severely deficient in vitamin D and its levels were inversely correlated with most of the components of metabolic syndrome.

Keywords: Vitamin D deficiency, Metabolic syndrome, Obesity, Type 2 diabetes mellitus. (JPMA 64: 1229; 2014)

Introduction

Non-communicable chronic diseases, which include cardiovascular diseases (CVDs), obesity and diabetes mellitus (DM), are the leading causes of morbidity and mortality and impose a great burden on healthcare delivery systems.[1] During a survey in Karachi it was found that every 4th middle-aged adult is suffering from coronary artery disease (CAD) in Pakistan.[2] Sedentary lifestyle, family history, dyslipidaemia and hypertension are important known risk factors which enhance the likelihood of DM and CVD. Metabolic syndroms (MetS) is also a very important risk factor for the development of CVD and DM.[3] According to the criteria,[4] revised in 2005, by the National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association (AHA), a patient is labelled as suffering from MetS when he/she is having at least 3 of the following 5 conditions: (a) Fasting blood glucose (FBS) ≥100mg/dl (or receiving drug therapy for hyperglycaemia), (b) blood pressure (BP) ≥130mmHg systolic and ≥85mmHg diastolic (or taking drugs for the treatment of hypertension), (c) waist circumference (WC) ≥88cm (35 inches) in women or ≥102 cm (41 inches) in Caucasian men — the cut-off values in Asians are: ≥80 cm (32 inches) in women or ≥90 cm (36 inches) in men, (d) Fasting serum triglycerides (TGs) ≥150mg/dl (or receiving treatment for elevated TGs), (e) high density lipoprotein (HDL) <40 mg/dl in men or <50mg/dl in women (or taking drug therapy for low HDL).

Adult Asians have lower WC, muscle mass, and body mass index (BMI) compared to white Caucasians.[5] Moreover, in adult South Asians, elevated TGs, hypertension, and hyperglycaemia appear at lower BMI (< 25kg/m^2) and at WC that otherwise is thought to be "normal". Asian Indians show higher resistance to insulin even when BMI is matched with other races.[6] It is no surprise that a number of healthy looking young adults have one or more than one components of MetS.[7] Improving the insulin sensitivity is vital to prevent the progress towards the occurrence of diabetes and its complications. Vitamin D may help treat DM and insulin resistance by affecting insulin secretion and its sensitivity by its actions on intracellular calcium.[8]

Vitamin D deficiency is a recently proposed risk factor for CVD and DM. Hypovitaminosis D has also been associated with obesity, dyslipidaemia, some cancers and many other communicable and non-communicable diseases.[9,10] Recent literature reports pandemic of vitamin D deficiency/insufficiency in very diverse populations.[9] It is anticipated that greater than one billion people all over the world have vitamin D deficiency. Most people with vitamin D deficiency/insufficiency are asymptomatic and

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hence it becomes a difficult entity to be detected.[10]

Research has revealed very low vitamin D levels in the Middle East and South East populations and it has been related to their lifestyle and clothing habits.[11] In Norway, Pakistani immigrants are more likely to be deficient in vitamin D than Norwegian natives.[12] Resident Pakistani population is also very deficient in Vitamin D. Prevalence of vitamin D deficiency of 92% and 81% has been reported in ambulatory subjects in Karachi and Lahore respectively.[13] Studies from India report 80-85% prevalence of vitamin D deficiency in postmenopausal women.[14] In healthy adults residing in urban Tehran, prevalence of vitamin D deficiency/insufficiency was about 80%.[15] Children and adolescents are also very likely to have hypovitaminosis D. For instance, in a study in Maine, USA, 48% of white pre-pubertal girls had less than 20ng/ml serum 25(hydroxyl [OH]) D.[16]

The current study was designed to determine serum vitamin D levels and its relation with the various components of MetS in adult non-diabetic offsprings of type 2 diabetic parents. An early detection of risk factors for CVD and DM may save a lot in terms of overall healthcare delivery mechanism, and may also improve future cardiovascular outcome.

Subjects and Methods

The analytical cross-sectional study was conducted from February to December 2012 at the Department of Physiology and Cell Biology, University of Health Sciences (UHS), Lahore. The subjects were recruited by convenient sampling method and were divided into four groups. Group A included non-diabetic, MetS positive offspring of type 2 diabetic parents; Group B had non-diabetic, MetS negative offspring of type 2 diabetic parents; Group C included non-diabetic, MetS positive offspring of non-diabetic parents; and Group D had non-diabetic, MetS negative offspring of non- diabetic parents.

Offspring whose both parents were diabetic were selected according to the inclusion criteria. Offspring of non-diabetic parents were recruited from the UHS, Allama Iqbal Medical College, Lahore, University of the Punjab, Lahore, and Amna Inayat Medical College, Sheikhupura.

Inclusion criteria for groups A and B were: (a) male and female non-diabetic subjects between 20-40 years age, (b) offspring of type 2 diabetic parents. Inclusion criteria for groups C and D were: (a) male and female non-diabetic subjects between 20-40 years age, (b) offspring of non-diabetic parents.

Exclusion criteria were: (a) subjects using calcium and multivitamin supplements, lipid-lowering drugs, anti-hypertensive drugs and steroids, (b) subjects having liver and kidney diseases; bone problems like osteoporosis and osteomalacia; endocrine disorders like Cushing syndrome, hyperthyroidism, hypothyroidism and hyperparathyroidism etc.,(c) pregnant females.

After written informed consent from each subject and approval from the institutional review committee were obtained, relevant personal and demographic information as well as medical history were taken. Complete general physical and systemic examination was conducted using standard methods. All the information obtained from the subjects was recorded on the subject data sheet.

After 12 hours of overnight fast, 4ml of venous blood was drawn by aseptic technique. FBS was measured by glucometer (Gluco Care). Blood collected in serum vials was centrifuged at 3000rpm for 10 minutes. Serum was transferred to properly labelled Eppendorf tubes and stored at -80°C until assayed.

Serum was assayed for TGs, total cholesterol (TC) and HDL by automatic chemistry analyser, Microlab 300. TG kit by Human Gesellschaft for Biomedica and Diagnostica D-65205 Wiesbaden-Germany, was used on the Merck Microlab 300 at 546nm. TG levels were measured by Glycerol Phosphate Oxidase-Peroxidase method. TC and HDL kits by Analyticon Biotechnologies AG Am Muehlenberg 10, 35104 Lichtenfels/Germany, were used. LDL was calculated indirectly by Friedewald's formula: LDL levels = TC - (TGs levels/5+HDL levels).Insulin and vitamin D were measured in human serum quantitatively by immunoenzymatic assay with an automated enzyme immunoassay analyser (EIA) (Bio-Rad, USA) with DIA source Kits (Belgium).Concentration of 25(OH) D <30ng/ml was accepted as insufficiency, <20ng/ml as deficiency and <10ng/ml as severe deficiency.[9] Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated: HOMA-IR = Fasting insulin (mIU/L) x Fasting glucose (mmol/L)/ 22.5.

Data was analysed using SPSS20. Mean Standard deviation (SD) was given for normally distributed quantitative variables and median interquartile range (IQR) for non-normally distributed quantitative variables. Two sample "t" test and Mann-Whitney U tests were used to compare the differences. Pearson and Spearman correlation tests were used to observe the correlations. A p-value ≤ 0.05 was considered statistically significant.

Results

A total of 88 subjects were included in the study;

Table-1: Comparison of various study parameters between offspring of type 2 diabetic and non-diabetic parents.

Parameters	Mean ± SD or Median (Q1 - Q3)		P-value
	Both parents diabetic (n=40)	Both Parents Non-diabetic (n=48)	
Body Mass Index (kg/m^2)	26.15 (23.18-29.57)	24.25 (19.94-28.75)	0.34
Waist/Hip ratio	0.88 ± 0.08	0.87 ± 0.08	0.52
Systolic BP (mmHg)	114.90 ± 11.51	117.06 ± 11.28	0.38
Diastolic BP (mmHg)	79.23 ± 11.07	78.88 ± 8.44	0.86
Fasting Serum TGs (mg/dl)	129 (89-159)	113 (73.25-163.50)	0.284
Fasting Serum HDL (mg/dl)	31.85 ± 5.53	32.23 ± 3.71	0.70
Fasting Serum LDL (mg/dl)	121.78 ± 30.29	114.83 ± 32.93	0.31
TC(mg/dl)	178.65 ± 27.25	170.90 ± 33.97	0.24
TG/HDL ratio	3.91 (2.56-4.82)	3.36 (2.36-5.18)	0.11
TC/HDL ratio	5.80 ± 1.33	5.37 ± 1.22	0.11
HDL/LDL ratio	0.26 (0.21-0.35)	0.28 (0.22-0.36)	0.38
Fasting Blood Sugar (mg/dl)	90.73 ± 17.31	90.96 ± 15.46	0.94
Fasting Serum Insulin (?IU/ml)	21.76 (12.90-24.46)	19.88 (11.44-25.30)	0.46
HOMA-IR	4.64 (2.64-6.34)	4.06 (2.36-6.05)	0.46
Serum Vitamin D (ng/ml)	8.41 ± 5.23	8.47 ± 4.15	0.95

BP: Blood pressure
TG: Triglycerides
HDL: High density lipoprotein
LDL: Low density lipoprotein
TC: Total Cholesterol
HOMA-IR: Homeostasis model assessment of insulin resistance.

Table-2: Summary of the parameters (mean results) of various study groups A, B, C, and D.

Study parameters	Group A n=20	Group B n=20	Group C n=23	Group D n=25
Age (years)	27.10 ± 5.51	25.20 ± 4.45	26.91 ± 6.93	24.96 ± 4.04
Body Mass Index (kg/m^2)	28.21 ± 3.81	23.48 (21.48-27.16)	30.11 ± 10.42	20.14 (18.30-22.02)
Waist/hip ratio	0.90 ± 0.08	0.86 ± 0.07	0.92 ± 0.07	0.83 ± 0.07
Systolic BP (mmHg)	117.90 ± 10.72	111.74 ± 11.73	120.30 ± 12.45	114.08 ± 9.37
Diastolic BP(mmHg)	82.15 ± 9.63	76.16 ± 11.88	81.48 ± 7.71	72.50 (70-83)
Fasting Serum TGs (mg/dl)	156.80 ± 34.59	98.15 ± 38.14	149.61 ± 56.94	85.50 (58.50-117)
TC (mg/dl)	182.70 ± 24.23	174.60 ± 30.05	175.91 ± 31.43	166.28 ± 36.17
Fasting HDL (mg/dl)	30.65 ± 4.18	33 (27-36)	32.91 ± 3.39	31.60 ± 3.97
Fasting LDL (mg/dl)	121.70 ± 25.07	121.85 ± 35.43	113.74 ± 31.54	115.84 ± 34.77
TG/HDL ratio	5.05 ± 1.45	3.00 ± 1.01	4.49 ± 1.86	2.70 (1.82-3.94)
TC./HDL ratio	6.06 ± 1.12	5.54 ± 1.51	5.39 ± 1.09	5.35 ± 1.35
HDL/LDL ratio	0.26 ± 0.07	0.29 ±0.11	0.31 ± 0.09	0.27 (0.20-0.34)
Serum Vitamin D (ng/ml)	8.54 ± 4.81	8.27 ± 5.73	9.84 ± 3.79	6.77 (4.1-8.89)
FBS (mg/dl)	99.30 ± 16.32	82.15 ± 13.92	92 (74.50-102.25)	91.92 ± 16.00
Fasting Serum Insulin (mIU/L)	24.31 ± 8.74	15.42 (7.06-24.12)	24.20 (20.20-30.22)	13.77 (9.59-19.83)
HOMA-IR	5.83 ± 2.25	3.16 ± 1.67	5.49 (4.07-6.62)	2.90 (2.02-4.25)

Mean ± SD or median (Q1 - Q3)
Group A= the non-diabetic, metabolic syndrome positive offspring of type 2 diabetic parents
Group B= the non-diabetic, metabolic syndrome negative offspring of type 2 diabetic parents
Group C= the non-diabetic, metabolic syndrome positive offspring of non- diabetic parents
Group D= the non-diabetic, metabolic syndrome negative offspring of non- diabetic parents.
BP: Blood pressure
TG: Triglycerides
HDL: High density lipoprotein
LDL: Low density lipoprotein
TC: Total Cholesterol
HOMA-IR: Homeostasis model assessment of insulin resistance.

Table-3: Correlation between serum vitamin D levels and various components of metabolic syndrome in study groups A, B, C, and D.

Study parameters	Group A n=20		Group B n=20		Group C n=23		Group D n=25	
	Correlation coefficient (r)	p-value	Correlation coefficient (r)	p-value	Correlation coefficient (r)	p-value	Correlation coefficient (r)	p-value
Systolic BP (mmHg)	0.23[a]	0.32	0.30[a]	0.21	0.05[a]	0.84	0.18[b]	0.38
Diastolic BP (mmHg)	0.14[a]	0.54	0.29[a]	0.22	0.05[a]	0.82	-0.03[b]	0.90
Fasting Serum TGs (mg/dl)	-0.05[a]	0.84	0.30[a]	0.19	0.39[a]	0.07	-0.05[b]	0.81
Fasting Serum HDL (mg/dl)	-0.06[a]	0.80	0.33[B]	0.15	0.19[a]	0.39	-0.34[b]	0.09
Fasting Serum LDL (mg/dl)	-0.44[a]	0.05*	-0.32[a]	0.17	-0.52[a]	0.01*	-0.15[b]	0.46
TC (mg/dl)	-0.47[a]	0.03*	-0.20[a]	0.40	-0.36[a]	0.09	-0.13[b]	0.52
TG/HDL ratio	-0.00[a]	0.99	0.08[a]	0.74	0.34[a]	0.11	0.05[b]	0.81
TC/HDL Ratio	-0.26[a]	0.27	-0.31[a]	0.18	-0.41[a]	0.05*	0.013[b]	0.86
HDL/LDL Ratio	0.35[a]	0.12	0.48[a]	0.03*	0.50[a]	0.02*	0.03[b]	0.88
Fasting blood sugar (mg/dl)	0.36[a]	0.12	-0.60[a]	0.00*	-0.46[b]	0.02*	0.10[b]	0.62
Fasting Serum Insulin (µIU/ml)	-0.09[a]	0.70	0.46[B]	0.04*	0.26[b]	0.24	-0.54[b]	0.01*
HOMA-IR	0.04[a]	0.85	0.24[a]	0.31	0.09[b]	0.69	-0.39[b]	0.05*

*Statistically significant;a= Pearson Correlation;b= Spearman Correlation.
Group A= the non-diabetic, metabolic syndrome positive offspring of type 2 diabetic parents
Group B= the non-diabetic, metabolic syndrome negative offspring of type 2 diabetic parents
Group C= the non-diabetic, metabolic syndrome positive offspring of non- diabetic parents
Group D= the non-diabetic, metabolic syndrome negative offspring of non- diabetic parents.
BP: Blood pressure
TG: Triglycerides
HDL: High density lipoprotein
LDL: Low density lipoprotein
TC: Total Cholesterol
HOMA-IR: Homeostasis model assessment of insulin resistance.

40(45.5%) were offspring of type 2 DM parents, and 48(54.5%) were the offspring of non-diabetic parents. After further classification, Group A had 20(22.72%) subjects, Group B had 20(22.72%), Group C had 23(26.13%) and Group D had 25(28.40%) subjects.

In terms of educational background, only 7 (8%) subjects were below matric, 4(4.55%) were matric, 13(14.77%) were intermediate, 31(35.2%) were graduates and 33(37.5%) were post-graduates. Low, middle and high socioeconomic status was seen in 14(15.9%), 68(77.3%) and 6 (6.8%) subjects respectively. Indoor jobs were seen in the case of 73 (83%) subjects, while 15 (17%) were working outdoors.

Mild and moderate physical activity was seen in 66(75%) and 22(25%) subjects respectively. History of mild and moderate sun exposure was present in 60(68.2%) and 28 (31.8%) subjects respectively. Most of the subjects had colour grades between 18-23 on von-Luschan's scale.

Various study parameters were noted at the outset and values were compared across the groups (Table-1), while descriptive statistics of the groups were also noted (Table-2).Correlation between serum vitamin D and various components of MetS in the groups were then worked out (Table-3). In Group A, significant negative correlation was observed between serum vitamin D and fasting serum LDL ($r = -0.44$; $p< 0.05$) and TC ($r = -0.47$; $p< 0.03$). In Group B, significant negative correlation was observed between serum vitamin D and FBS ($r = -0.60$; $p< 0.01$) while significant positive correlation was observed between serum vitamin D and HDL/LDL ratio ($r = 0.48$; $p< 0.03$) and fasting serum insulin ($r = 0.46$; $p< 0.04$). In Group C, significant negative correlation was observed between serum vitamin D and fasting serum LDL ($r = -0.52$; $p< 0.01$) and FBS ($r = -0.46$; $p< 0.02$), while significant positive correlation was observed between serum vitamin D and HDL/LDL ratio ($r = 0.50$; $p< 0.02$). In Group D, significant negative correlation was observed between serum vitamin D and fasting serum insulin ($r = -0.54$; $p< 0.01$) and HOMA-IR ($r = -0.39$; $p< 0.05$).

Discussion

The study found that vitamin D levels were disappointingly low in adult non-diabetic study subjects. Vitamin D deficiency (<20ng/ml) was prevalent in 98.5% of the study subjects and 87.5% of the subjects had vitamin D levels <15ng/ml. Severe deficiency (<10ng/ml) was seen in 70% of the subjects. Considering the fact that most of the subjects were asymptomatic healthy adults, it raises serious concern that most of the healthy population may be deprived of the established benefits of vitamin D.

This prevalence of vitamin D deficiency is higher than previously reported values from various regions of Pakistan and neighbouring countries. This may be explained by the fact that 83% of the study subjects had indoor jobs, 75% subjects had mild physical activities and 68% of the subjects had mild sun exposure. Sedentary lifestyle, minimal physical activity and lack of sun exposure all contribute to hypovitaminosis D.[9] Lack of food fortification with vitamin D and consumption of traditional diet deficient in vitamin D are amongst the dietary factors that contribute to vitamin D deficiency. In addition, none of the subjects in the study was using vitamin D supplements. Traditional and religious clothing habits and lifestyle is also responsible for vitamin D deficiency, particularly in women.[11] In Pakistan, most of the people, especially females, because of their religious beliefs, wear such a dress that most of the skin is shielded from sunlight, thus preventing the synthesis of vitamin D. Increasing urbanisation and industrialisation may also reduce exposure to sunlight. Darker skin colour in the local population may also hinder proper penetration of ultraviolet-B (UV-B) rays required for vitamin D synthesis. All this necessitates increased dietary intake of vitamin D and increased exposure to sunlight.

No significant difference in the vitamin D levels was observed between the offspring of type 2 diabetics and the offspring of non-diabetic parents. Since our sample size was quite restricted, a greater sample size may have shown a significant difference. However, our other unpublished data from around 500 subjects taken from local population clearly shows that the levels encountered in the present study are representative of the local population. Secondly, we assume that low vitamin D levels encountered in the present study have confirmed the results further.

In this study, inverse correlation was observed between serum vitamin D and fasting serum LDL, TC and TC/HDL ratio, FBS, while positive correlation was observed between serum vitamin D and HDL/LDL ratio in the groups. These findings are consistent with those of earlier works.[8,9,18,19]

The mechanistic role of hypovitaminosis D in dyslipidaemia and insulin resistance is not well understood. Cross-sectional studies undertaken to date could not clarify whether vitamin D deficiency is the cause or effect of dyslipidaemia and insulin resistance. In one study,[19] 126 glucose tolerant, healthy subjects were enrolled for the assessment of relation of serum vitamin D with the insulin sensitivity index (ISI) and beta cell function. Insulin sensitivity was measured by hyperglycaemic clamp method. After regression analyses, it was revealed that vitamin D was positively correlated with ISI and there was a negative effect of vitamin D deficiency on the function of beta cells. Insulin resistance is the fundamental factor which leads to atherogenic dyslipidaemia. Insulin resistance is the intermediate link between obesity and CVDs. Therefore, it is important clinically to identify those overweight persons who are insulin resistant so that measures may be undertaken to prevent the chances of development of CVDs.[20] Over-secretion and catabolism of TG-rich very low density lipoprotein (VLDL), is the cause of this altered lipoprotein pattern in obese and insulin resistant cases.[21]

Another interesting finding in our study was that except only two males, all the subjects had low HDL levels. This is alarming as low HDL is a known risk factor for the development of atherosclerosis. In an earlier study, higher HDL levels than ours were found in young Polish women with and without MetS.[22] May be the South Asians are genetically predisposed to have comparatively lower levels of HDL or their normal reference values of these metabolites are lower than those of Caucasians.

Another important observation made in the present study was higher insulin resistance seen in the subjects. Gold standard for determination of insulin resistance is euglycaemic insulin clamp but it is not feasible in population-based studies and in clinical practice. Therefore, we used HOMA-IR as the standard method to determine insulin resistance. Median HOMA-IR levels were 5.73 (4.07-6.75) and 3.01 (1.98-4.61) in subjects with and without MetS respectively. A study[22] found median HOMA-IR of 2.9 (1.9 - 4.4) and 1.2 (0.9-2) in young women with and without metabolic syndrome respectively. This raises the serious concern that young study population is more insulin resistant and more prone to developing diabetes in later age than Western population. Further studies in this direction are needed which may point towards the reason underlying the increasing numbers of people visiting the diabetic clinics of Pakistan.

No significant difference was found in the components of MetS between the offspring of type 2 diabetics and the offspring of non-diabetic parents in the present study. Although the risk of obesity and MetS is more common in the offspring of type 2 diabetics,[23] but it was found in our study that if age, gender and BMI are matched, the components of MetS in the adult non-diabetic offspring of type 2 diabetics are not different than those found in the offspring of non-diabetic parents.

The study had its limitations. It was an analytical cross-sectional study which does not provide information

whether vitamin D deficiency is the cause or effect of other cardio-metabolic risk factors. Cohort studies and randomised controlled trials are required to have knowledge on causalities. Due to limited resources, the study had a limited sample size which was further divided into 4 groups. In order to get better insight, the sample size needs to be increased. Serum calcium and Parathyroid hormone (PTH) levels are very closely related to serum vitamin D level. But, serum calcium and PTH levels were not included because of limited funds. Lack of global consensus on biochemical definition of vitamin D deficiency was another limitation. Some studies have used 20ng/ml as the cutoff point, while others have used 15ng/ml. In this study, a cutoff value of <20 ng/ml was used. On this scale, vitamin D deficiency was seen in 98.5% of the study subjects when vitamin D <20ng/ml was used as the cutoff level, while 87.5% subjects had vitamin D levels <15ng/ml.

We recommend that since vitamin D deficiency was very common in the study population, 25-OH vitamin D levels should be checked at mass level. Genetic studies should be conducted to check polymorphism in the genes involved in the activation and deactivation of vitamin D. Food items should be fortified with vitamin D at a large scale and food manufacturers should be encouraged in this regard. As HDL was low in majority of the study population, genetic studies should be conducted to check the genetic associations.

Conclusions

Majority of the study population was deficient in vitamin D. Vitamin D deficiency is also associated with most of the components of MetS in local population, but no significant difference in vitamin D levels was found between the offspring of type 2 diabetics and the offspring of non-diabetic parents. High insulin resistance was present in the adult non-diabetic subjects.

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