의학 박사학위 논문

Waist Circumference Is The Key Risk Factor for Diabetes in Women with Previous History of Gestational Diabetes

아 주 대 학 교 대 학 원

의 학 과

홍 은 경

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이 논문을 의학 박사학위 논문으로 제출함.

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2002 년 12 월 20 일

감사의 글

어느새 시간의 흐름이 물과 같다는 말에 공감이 가는 때가 되어버렸습니다. 3년전 석사학위를 마치고 지방으로 내려가게 되었을 때 박사학위를 시작하는 일이 커다란 부담으로 만 여겨졌었습니다. 그때 저에게 커다란 희망과 용기로 답을 주시며 흔쾌히 받아주셨고 어려운 여건 속에서도 세심한 부분까지 마음 써 주신 저의 지도교수 조남한 교수님께 진심으로 감사를 올립니다. 바쁜 중에도 항상 웃으며 논문 자료 정리와 통계를 도와주신 홍순성 선생님과 역학센터 여러 선생님들, 매주 수원에 가는 일로 병원을 비우게 되는 날에도 밝은 모습으로 격려해 주시고 흔쾌히 보내주신 유재명 교수님과 한림대 강남성심병원 내과 교수님들께도 감사 드립니다.

이렇게 힘든 일은 이제 마지막이면 좋겠다는 생각을 항상 해보지만 끊임없이 반복되는 삶의 전쟁속에서 가지게 되는 생각이 있습니다. 어려움에 처해보지 않은 사람은 자신의 주변에 얼마나 많은 고마운 분들이 있는지 모른다는 사실입니다. 그럴 때마다 항상 저에게 힘이 되어 주신 큰 언니 같은 최선정 선생님, 홀로서기를 하며 살아야 했던 여러 해를 뒤로하고 부모님과 같은 사랑을 주시는 강성구 교수님께 진심으로 감사를 드립니다.

지금의 제가 있을 수 있도록 내분비의 시작을 마련해 주셨던 아주대 내분비내과 김현만 교수님, 정윤석 교수님, 학위논문 심사와 마무리까지 힘들고 바쁘신 중에도 마다 않으시고 끝까지 챙겨주신 이관우 교수님, 이경종 교수님, 그리고 구미라는 멀고도 가까운 곳으로 첫 교원 발령을 받고 내려가 있는 동안 커다란 의지의 버팀목이 되어 주셨던 조용욱 교수님과 지금은 고인이신 성차경 부장님께도 감사의 마음을 전합니다. 무얼 하는지 항상 바쁘다는 핑계로 연락조차 잘 하지 못하는 이 친구를 언제나 사랑과 격려로 지켜봐 주고 챙겨주는 사랑하는 나의 친구들, 먼 곳에 있지만 마음 가운데 자리잡고 있는 착하고 사랑스런 동생이자 동료인 노혜림, 김윤정, 김효정, 그리고 말없이 저의 곁에서 항상 격려와 믿음으로 지켜봐 주시고 아껴 주시는 보든 분들께도 감사를 보냅니다.

이제는 제게도 먼저 배운 선배로써 후배들에게 무엇인가를 남겨주어야 한다는 커다란 짐의 무게가 어깨 위에 놓여 있음을 느낍니다. 이들에게 최선을 다하는 또한 저의 삶에 최선을 다하도록 노력하는 자신이길 바라면서

끝으로 자신의 삶의 대부분을 자식들에게 바치신 사랑하는 어머니와 세상의

여러 어려움 속에서도 꿋꿋하고 착하게 살아가는 우리 가족들, 오래전 사랑하는 사람들을 남겨두고 힘겹게 떠나가셨을 우리 아버지, 지금 이 글을 보지는 못하지만 유난히 저에게 자신과 같은 길을 가는 교수이길 바라시던 큰 오빠, 그리고 길고도 짧은 세월에 끊어질 수 없는 인연으로 만나 이제 새로운 나의 반쪽이 될 오빠와 새로운 부모님, 가족들께 이 논문을 바칩니다.

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저자 씀.

Waist Circumference Is The Key Risk Factor for Diabetes in Women with Previous History of Gestational Diabetes

by

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- ABSTRACT -

Waist Circumference Is The Key Risk Factor for Diabetes in Women with Previous History of Gestational Diabetes

Purpose: Many women with previous history of gestational diabetes mellitus (GDM) convert to insulin dependent diabetes mellitus (IDDM) or mainly non-insulin dependent diabetes mellitus (NIDDM) during postpartum follow-up period. Some related factors which influenced postpartum diabetes mellitus such as obesity, family history of diabetes mellitus, prepregnancy body weight, age of mother, weight gain during pregnancy, parity, and previous history of GDM were previously reported. Among these risk factors of postpartum NIDDM, a wide variety of obesity measurements were thought to be associated with an onset of NIDDM after GDM. Therefore, the purpose of our study is to investigate the relationships between the obesity indices and an onset of NIDDM in Korean women with a previous history of GDM.

Subjects & Methods: A total 909 subjects with previous history of GDM were recruited and longitudinal annual examination was made over the 6 years postpartum period. The first postpartum follow-up examination was made at 6 weeks, and an annual follow-up was done thereafter. In antepartum, we examined the pre-pregnancy clinical characteristics, the family history, dietary, habitual, exercise, and the results of antepartum 100-g oral glucose tolerance test (OGTT). During

postpartum follow-up period, we performed 2 hours 75-g OGTT and measured the blood glucose, insulin, c-peptide, fasting lipid profiles, and obesity parameters such as body weight, body mass index (BMI), waist and hip circumference, subcutaneous fat thickness, body fat percent and weight by using bioelectrical impedance test, as well as lifestyle factors and dietary pattern.

Results: A total 12.8 percent (116/909 women) of women with a previous history of GDM was converted into diabetes mellitus during 6 years postpartum periods. Mean age and parity were very similar among normal glucose tolerance group (NGT), impaired glucose tolerance group (IGT), and DM group. However, family history of diabetes in DM subjects (55.2%) was significantly ($p<0.01$) higher than IGT and DM group. From the result of antepartum glucose metabolism assessment by 100-g OGTT, fasting, 1-, 2-, and 3-hour glucose concentration after glucose loading were significantly higher in DM group. All obesity indices in women with diabetes or glucose intolerance were significantly higher than normal women ($p<0.001$). Furthermore, this study also revealed that all the obesity parameters used in this study was significantly associated with the risk factors for diabetes macrovascular disease.

Although, a positive correlation was observed among waist circumference, subscapular skin fold thickness, body fat weight, BMI and blood glucose level ($r=0.21$, 0.20, 0.20, 0.19, respectively), the most significant relationship was seen between waist circumference and blood glucose level ($r=0.21$, $p<0.01$). However, when we stratified the levels of obesity indices according to the percentiles and

compared between <25th to >75th percentile, waist circumference among the eight significant obesity indices showed the highest relative risk (relative risk=5.8, 95% CI 2.8 11.8). When the potential confounders such as blood pressure, lipid profiles, age and duration of follow-up were adjusted by using multiple logistic regression analysis, relative risk (RR) of waist circumference persisted as the independent variable with RR=3.86 (95% CI 1.8~8.2). During follow-up periods, 14 of NGT and 16 of IGT subjects converted to DM and 46 of NGT subjects converted to IGT (W= worsened group). However, 23 of IGT and 11 of DM subjects converted to NGT and 4 of DM subjects converted to IGT (I=improved group). Six obesity indices such as body weight, BMI, suprailiac and subscapular skin fold thickness, hip circumference, and body fat weight accompanied with LDL-cholesterol concentration were significantly decreased in improved group when compared to the worsened group.

Conclusion: This prospective study revealed that obesity index such as the waist circumference is one of the key risk factors for an onset of diabetes in Korean women who had a previous history of GDM.

Key Words: NGT, normal glucose tolerance; IGT, impaired glucose tolerance; GDM, gestational diabetes mellitus

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I. INTRODUCTION

A. Definition and subclassification of GDM

GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy.[1] GDM may complicate as many as 2 to 6% of pregnancies in North American population, making it over 10 times as common as pregestational diabetes and a potentially serious public health problem.[2-3] Moreover, higher figures, as high as 20%, have been reported when liberal diagnostic criteria for GDM have been used and in some racial and ethnic.[4]

GDM is subclassified to distinguish between those with fasting plasma glucose (FPG) within the normal range for pregnancy and those with values exceeding the normal limits. Classification of carbohydrate intolerance during pregnancy are shown as below:

1. GDM

(A) GDM class A_1 : fasting glucose normal for pregnancy

venous plasma < 105 mg/dL (5.8 mmol/L)

(B) GDM class A_2 : fasting glucose exceeds normal for pregnancy

venous plasma ≥ 105 mg/dL (5.8 mmol/L) but < 130 mg/dL

(C) GDM class B : fasting glucose exceeds normal for pregnancy

venous plasma ≥ 130 mg/dL (7.2 mmol/L)

2. Previous GDM : abnormality of glucose tolerance in a previous pregnancy

without DM having been diagnosed postpartum

3. **Pregestational diabetes mellitus** : DM diagnosed according to NDDG criteria when not pregnant

   (A) Type I DM (IDDM)

   (B) Type II DM (NIDDM)

B. Etiology and pathophysiology

1. Phenotypic heterogeneity

Phenotypic heterogeneity includes differences in maternal age and weight, the severity of carbohydrate intolerance, and the degree of insulin secretion. Patients with GDM are older and heavier than their normal counterparts, but the spectrum of the age and weights are within the obstetrical population. Fasting plasma glucose levels tend to increase in parallel with the degree of obesity in GDM, but lean women with elevated FPG levels are frequently encountered. Fasting plasma insulin level is greater in the obese (≥ 120% of ideal) of both control and GDM groups (except in those GDM subjects with elevated FPG).

2. Genotypic heterogeneity

Genotypic heterogeneity in GDM is demonstrated by increased frequencies of HLA haplotypes, which have been associated with increased risk of IDDM, when compared with racially matched controls. Racial and ethnic group differences in prevalence of GDM have been observed and it is not fully accounted for by differences in maternal age or obesity.[5] Therefore, the specific mechanisms for

genetic predisposition for the majority of women with GDM remains to be defined.

3. Pathophysiology

Uncomplicated pregnancy is characterized by insulin resistance and enhanced insulin secretion as a compensatory mechanism to maintain the normal glucose tolerance (NGT).[6,7] However, a various previous reports indicated that in GDM subjects the decreased insulin sensitivity and more pronounced insulin resistance phenomena is occurring. These phenomena might contribute to hyperglycemia in addition to defective insulin release.[8]

C. Magnitude of the problem

1. Implications for the offspring

Many studies indicated that the increased risks of embryopathy and spontaneous abortion in pregnancy complicated by diabetes mellitus were related to metabolic disturbances around the time of conception.[9] However, neither the specific aspect nor the duration of metabolic abnormality responsible for the dysmorphic events are known.

A number of the adverse effects of diabetes that develop in the last half of gestation might result from increased delivery of nutrients to the fetus which provoked hyperinsulinemia and augmented fetal growth.[10] Fetal insulin secretion was increased as early as 16 weeks' gestation in poorly controlled diabetes. We have found a stronger association between fetal islet function and metabolic control in the second trimester than in the third trimester. As a consequence, macrosomia is a

frequent complication of GDM. The converse of macrosomia, intrauterine growth retardation (IUGR), also was reported in the past as a frequent complication of maternal diabetes. Two dramatic clinical findings have been noted with respect to birth weight in recent reports. IUGR is now a rare event among offspring of diabetic mothers, except when complicated by nephropathy and/or hypertension, and the frequency of macrosomia in offspring of mothers with pregestational DM has increased, reaching proportion as high as 30-40%.[11]

Fetal hyperinsulinemia also plays a critical role in the delayed pulmonary maturation and polycythemia that have been observed commonly in infants of diabetic mothers(IDM).[12,13] Heightened insulin secretion in the early postpartum period contributes to decreased glucose production, increased glucose disposal, and hypoglycemia that are frequently seen in IDM.[14]

Increasing evidence indicates that intrauterine development in the metabolic environment of maternal diabetes also may have long-term implications for the offspring. The possibility of long-term neurological deficits in offspring of diabetic mothers has been recognized for a number of years.[9] A number of investigators have reported a high prevalence of obesity and NIDDM in offspring of diabetic mothers (Fig. 1).[15]

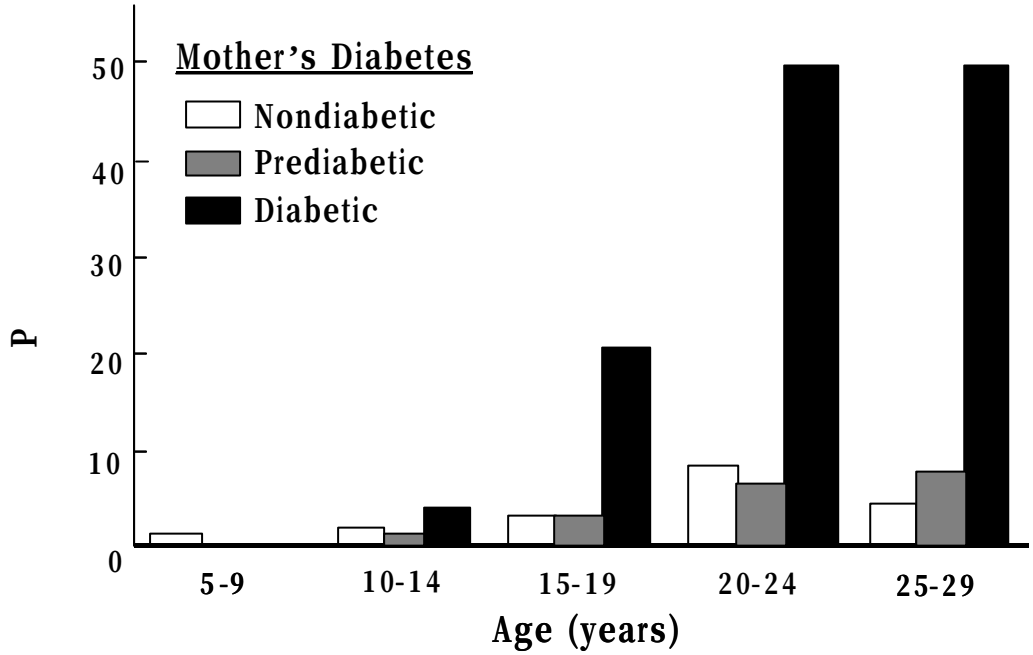


Fig. 1. Age-specific prevalence of NIDDM in offspring Pima Indian women without diabetes mellitus, those developing diabetes during only subsequent to pregnancy, or those with diabetes during pregnancy.

2. Implications for the postpartum follow-up of mother

Women with previous history of GDM have been considered as the high-risk group for diabetes mellitus (Fig. 2).[16] Thus, increasing public and scientific awareness of the prevalence, socioeconomic impact, and mechanisms of NIDDM has prompted continuous efforts to target the high-risk groups for interventions to prevent or delay the development of diabetes.[17] Several studies have shown that the prevalence of DM after GDM varies in wide range: Kjos et al. reported with 47%,[16] Metzger et al. 50%,[18] Damm et al. 3-65%,[19] Steinhart et al. 53%,[20] and Ali et al. with

62%.[21] This variability might be related to the ethnic variation, lack of uniformity in diagnostic criteria for GDM, diversity in follow-up care, characteristics of women lost to follow-up, and differences in statistical management of data.[22]

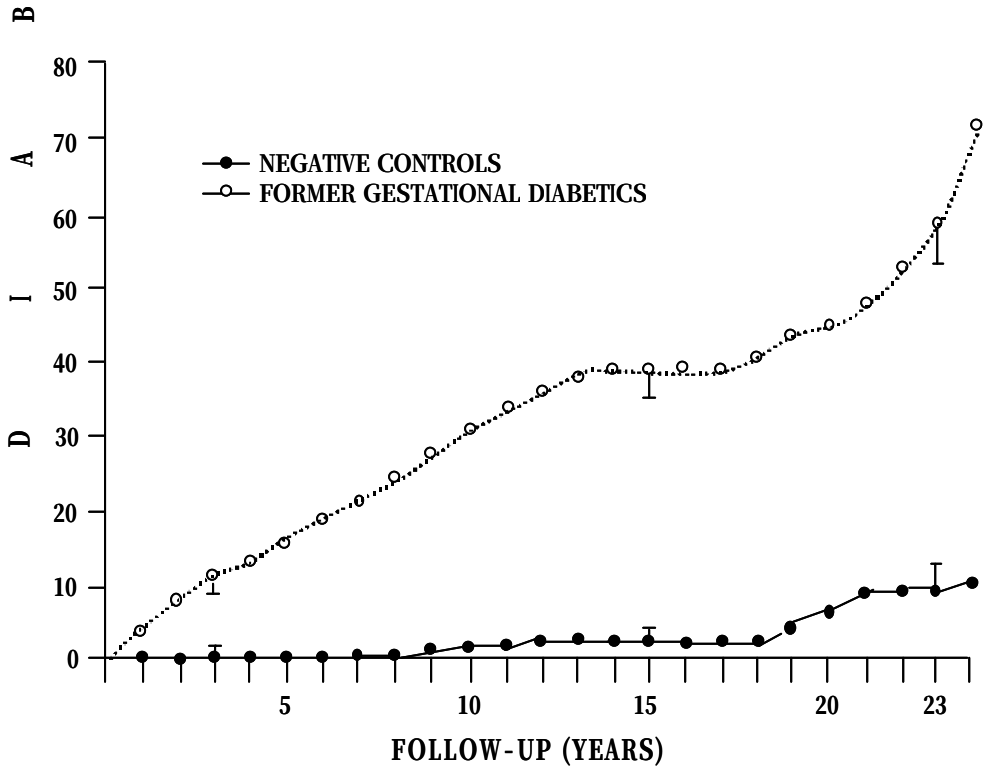


Fig. 2. Cumulative incidence of diabetes mellitus following pregnancy for women with gestational diabetes mellitus and women without gestational diabetes.

D. Diagnostic criteria of obesity parameters

1. Body mass index (BMI)

Classification	BMI (kg/m^2)
Low weight	< 18.5
Normal weight	18.5~22.9
Overweight	> 23
Risk	23~24.9
1^{st} grade obesity	25~29.9
2^{nd} grade obesity	> 30

2. Waist circumference and waist/hip ratio

Classification	Waist circumference (cm)		Waist/Hip ratio	
	Female	Male	Female	Male
Normal	< 80	< 90	< 0.8	< 1.0
Obesity	≥ 80	≥ 90	≥ 0.8	≥ 1.0

3. Skin fold thickness

Calculate from sum of two sites skin fold thickness

(upper forearm + subscapular)

Classification	Female (mm)	Male (mm)
Mild obesity	> 46	> 30
Moderate obesity	> 60	> 37
Severe obesity	> 74	> 43

4. Bioelectrical impedence

Classification	Female (%)	Male (%)
Normal	< 30	< 25
Obesity	³ 30	³ 25

E. Purposes of the study

GDM is one of the most common complications of pregnancy and at increased risk for NIDDM, also associated multiple antepartum complications. Many risk factors for the high incidence of DM after GDM were identified among the various ethnic groups. Obesity was one of the known risk factor for NIDDM after GDM.[23,24] However, it is not clear what type of obesity parameters and magnitude of obesity was associated with an onset of diabetes in this high-risk population. Therefore, in this multi-centered prospective study, we evaluated the incidence of diabetes and the relationships between the various obesity indices and an onset of diabetes in Korean women who had a previous history of GDM.

II. SUBJECTS AND METHODS

A. Study population and diagnostic criteria of GDM

This research was conducted in the four major general and university hospitals in Korea. The study subjects were recruited from August 1995 to May 1997. During 24-26 weeks' gestation, we performed 1 hour 50-g screening and followed by 3 hour oral glucose tolerance test (OGTT) if 1-hour glucose value was ≥130 mg/dl. The NDDG criteria was used to diagnosis GDM (Table 1).[25] In order to evaluate the risk factors and DM status, the initial examination was made at 6 weeks postpartum and annual follow-up examinations thereafter. We confirmed that there was no homogeneity or selection bias. Of 2,300 registered GDM subjects, 909 were randomly selected by using simple random selection method and asked to participate to the study. The mean yeas of follow-up was 2.3 ± 1.9 years.

Table 1. Diagnostic criteria for gestational diabetes mellitus

1) Administration of 100-g oral glucose load the morning after overnight fast of at least 8 but no more than 14 hours and after at least 3 days of unrestricted diet (≥150g of carbohydrate) and physical activity
2) Plasma glucose is measured fasting and at 1, 2, and 3 hours after the oral glucose load (subject should remain seated and should not smoke throughout the test)
3) Two or more of the following venous plasma glucose concentrations must be met or exceeded for a positive diagnosis.
   - Fasting, 105 mg/dL (5.8 mmol/L)
   - 1 hour, 190 mg/dL (10.6 mmol/L)
   - 2 hour, 165 mg/dL (9.2 mmol/L)
   - 3 hour, 145 mg/dL (8.1 mmol/L

B. Questionnaire evaluation

During the initial and annual follow-up evaluation, all participants life style, dietary intake, family history of diseases, medical and reproductive history, socioeconomic status, educational level, and habitual factors were interviewed using the standardized questionnaire by the trained interviewers. Face-to-face interview method was used.

C. Laboratory assessment

After 8-14 hours overnight fasting, all participants underwent 2 hours 75-g OGTT. The NDDG diagnostic criteria were used to diagnose DM during the postpartum follow-up period (Table 2). During the OGTT, fasting, 30 minutes, 1 hour, 90 minutes, and 2 hours blood samples were obtained by venipuncture from antecubital veins. Serum and red blood cells were separated by centrifugation at 1900 x *g* for 15 min. The serum was transferred to plastic labeled vials and frozen at -70°C before the measurement of serum insulin and c-peptide level. However, plasma glucose level was measured immediately after the blood drawn by using glucose oxidase method (YSI 2300-STAT; Yellow Springs Instrument Co., Ohio). Plasma insulin and c-peptide levels were measured using radioimmunoassay kits (Linco research Inc., St. Louis, MO). Blood samples were also sent to the hospital central laboratory immediately to analyze the lipid profiles. Total cholesterol and triglyceride concentrations were determined by enzymatic procedures in serum with a Beckman analyzer (Beckman Instruments, Brea, CA). High-density-lipoprotein

cholesterol (HDL-cholesterol) levels were determined using the direct EZ-HDL Sigma assay, which uses anti human 9-lipoprotein antibody to bind with low-density-lipoprotein cholesterol (LDL-cholesterol), very-low-density-lipoprotein cholesterol (VLDL-cholesterol), and chylomicrons (Sigma Diagnostics, St. Louis, MO). HDL-cholesterol levels can then be directly analyzed by enzymatic procedures. LDL-cholesterol was calculated from total cholesterol, triglyceride, and HDL-cholesterol by using the Friedwald equation.[26] Blood pressure (BP) measurement was made 3 times at the supine position after 10 minutes rest. Two minutes rest period was given during the each measurement.

Friedwald equation:

LDL cholesterol = Total cholesterol – (triglyceride/5) – HDL cholesterol

Table 2. Diagnostic Values for the Oral Glucose Tolerance Test (NDDG)

	Glucose Concentration, mmol/L (mg/dL)			
	Whole Blood		Plasma	
Diagnosis, Test	Venous	Capillary	Venous	Capillary
DM				
Fasting value	≥6.7 (≥120)	≥6.7 (≥120)	7.8 (≥140)	≥7.8 (≥140)
or				
2hr after glucose load	≥10.0(≥180)	≥11.1(≥200)	≥11.1(≥200)	≥12.2(≥220)
IGT				
Fasting value	<6.7(<120)	<6.7(<120)	<7.8(<140)	<7.8(<140)
and				
2hr after glucose load	6.7-10.0 (120-180)	7.8-11.1 (140-200)	7.8-11.1 (140-200)	8.9-12.2 (160-220)

D. Anthropometric evaluation

Anthropometric evaluation was done at every follow up day for 75-g OGTT. Body weight and height were measured in light clothing without shoes. To measure the obesity level, we applied a various methods such as body mass index (BMI), waist and hip circumference and ratio, body fat percent and weight by the bioelectrical impedence method (Body Composition Analyzer, Giru co., Korea), and skin fold thickness at four sites. The inter- and intra observer validity were confirmed by the repeated testing of the same subjects by the same and different observes. The ANOVA and Pearson correlation was used at the level of P-value <0.05 to demonstrate the statistical significance. To calculate the body mass index (BMI), height and weight measurement was made on a bare-footed and in a light clothing. BMI was calculated by dividing weight in kg by height in m^2. Waist circumference (WC) was measured at the level of the umbilicus, and the hip circumference (HC) was measured at the level of the greater trochanters. Skin fold thickness including biceps, triceps, subscapular, and suprailiac region was measured using Lange skin fold carliper.[27]

E. Mathematical model

Using the insulin and glucose values from the 75-g OGTT data, pancreatic beta-cell function and insulin resistance were calculated by HOMA model. Area under the curve (AUC) for glucose, insulin and c-peptide was calculated by the trapezoidal method. Mathematical model to calculate AUC, beta-cell function and

insulin resistance is as follows:

AUC = [(fasting + 120min)/4] +[(30min + 60min + 90min)/2]

Beta-cell function = (20 x basal insulin)/[basal glucose (mg/dl)/18-3.5]

Insulin resistance = basal insulin/22.5exp(-ln.fasting glucose/18)

F. Statistical analysis

Statistical analyses were conducted using SPSS Window 10.0. Data were expressed as means ± standard deviation. The study subjects were stratified into the three subgroups (NGT=normal glucose tolerance, IGT=impaired glucose tolerance, DM=diabetes mellitus) according to the NDDG criteria for the analysis (Table 2).[25] The statistical significance of differences among groups was evaluated using the student t-test and ANOVA. Differences were considered as statistically significant when P-values were <0.05. Relative risks of data were analyzed using logistic regression, with postpartum DM status as the dependent variable and obesity measurements including WC as independent variables. A stepwise multiple logistic regression analysis was used to evaluate independent effects of the potential risk factors and an onset of DM during the postpartum period.

III. RESULTS

A. Demographic characteristics of study population

During the 6 years postpartum follow-up, 116 (12.8%) and 120 (13.2%) subjects out of 909 total participants were converted to either DM or IGT respectively (Table 3). And cumulative incidence of DM during 6-year follow-up periods was 46.8% (Fig. 3). For the analyses, we used the measurements at the time of first diagnosis of DM or IGT but the most recent measurement was used for Normal.

Table 3. Incidence of NGT, IGT and DM subjects during follow-up periods

	NGT (n)	**IGT** (n)	**DM** (n)	**Total**
6 weeks	228	39	36	303
1 year	99	20	25	144
2 years	96	21	26	143
3 years	115	18	19	152
4 years	82	13	6	101
5 years	23	3	1	27
6 years	30	6	3	39

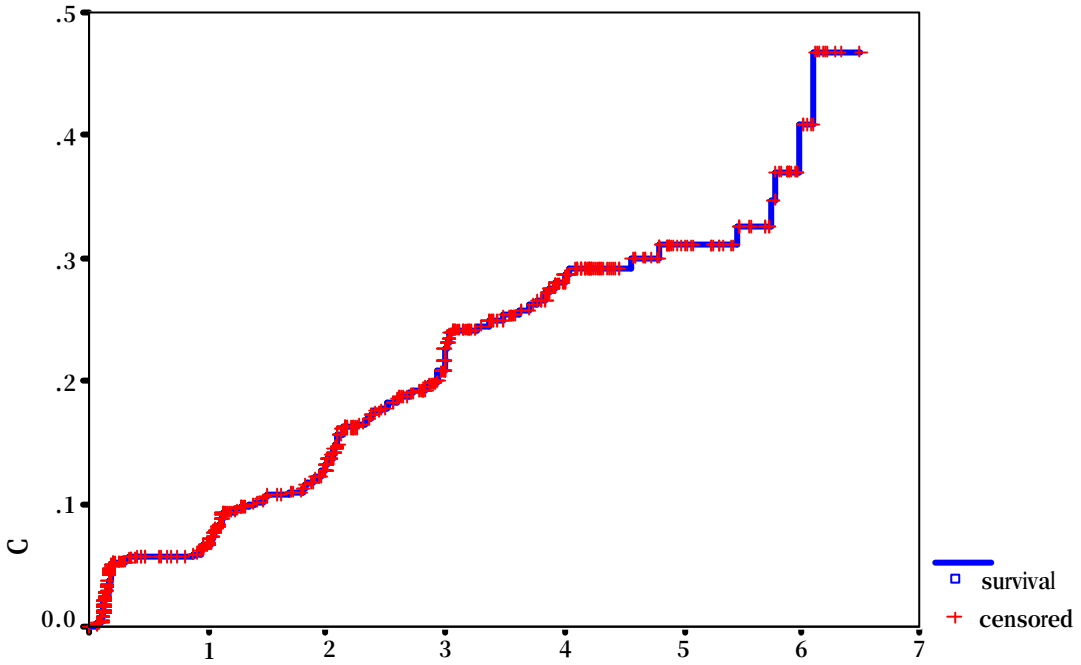


Fig. 3. Cumulative survival rate from DM. Cumulative incidence of DM during 6-years of follow-up period was 46.8%.

Demographic characteristics of the study population are summarized in Table 4. Mean age and parity were very similar among the three study subgroups. However, family history of diabetes in DM subjects (55.2%) was significantly ($p<0.01$) higher than the NGT or IGT subjects with 39.8% and 49.2% respectively. A positive family history of DM in either mother or father was more than 70% in this study population. Furthermore, family history of DM in either mother or father was more frequent in DM group (42.2%, 42.2%, respectively) than the NGT group (35.8 study %, 38.4%, respectively). When we compared working status and onset of diabetes, we found no relationships. However, when we adjusted for the putative risk factors such age, waist/hip ratio (WHR), and biceps skin fold thickness using multiple logistic

regression analysis, the onset of diabetes after GDM was significantly higher in women with an occupation than a housewife ($p<0.001$). We found no significant differences in other factors such as drinking, smoking, and degree of education among the groups.

Table 4. Demographic characteristics at final diagnosis of glucose tolerance

	NGT (n=673)	**IGT** (n=120)	**DM** (n=116)	**P value**
Age (years)	33.2 ± 4.7	34.2 ± 4.4	33.0 ± 4.2	NS
Parity (%)				NS
n = 1	262 (39.0)	45 (37.8)	46 (39.7)	
n = 2	345 (51.4)	66 (56.9)	66 (56.9)	
n > 3	64 (9.5)	4 (3.4)	4 (3.4)	
Family history (%)	268 (39.8)	59 (49.2)	64 (55.2)	< 0.01
Mother	96 (35.8)	24 (40.7)	27 (42.2)	
Father	103 (38.4)	22 (37.3)	27 (42.2)	
Siblings	19 (7.1)	3 (5.1)	5 (7.8)	
Others	50 (18.7)	10 (16.9)	5 (7.8)	
Occupation (%)				NS
Yes	475 (70.6)	83 (70.3)	94 (81.0)	
No	198 (29.4)	35 (29.7)	22 (19.0)	

NS = not significant

B. Results of 100-g OGTT at diagnosis of GDM

From the result of antepartum glucose metabolic assessment by 100-g OGTT, fasting, 1-, 2-, and 3-hour glucose concentration after glucose loading were significantly high in DM group ($p<0.001$, Fig.4).

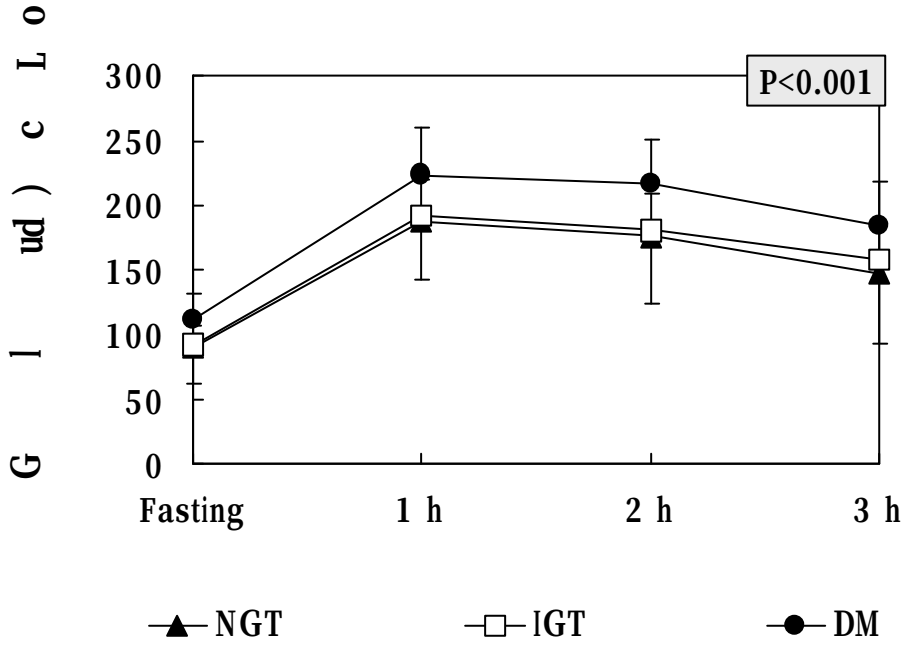


Fig. 4. Glucose profiles of 100-g OGTT at diagnosis of GDM. From the result of 100-g OGTT at diagnosis of GDM, all glucose concentrations were significantly high in DM group compared with NGT or IGT group ($p<0.001$).

C. Analysis of correlation between the status of glucose tolerance and the risk factors for diabetes mellitus

Correlations between the status of diabetes (NGT, IGT, DM) and the putative risk factors including clinical characteristics, lipid profile, and variables of obesity measurements were analyzed using the Pearson correlation (Table 5).

Blood pressure, family history of diabetes, total cholesterol, triglyceride, and LDL-cholesterol variables were all positively associated with diabetes status ($p<0.01$). However, HDL-cholesterol showed significant and a negative correlation ($p<0.01$). All variables of obesity measurements showed significant and a positive correlation with the diabetes status($p<0.05$). Furthermore, parameters of the all obesity variables were positively correlated with most of the glucose, insulin, c-peptide and the lipid variables exception of HDL-cholesterol. HDL-cholesterol was a negatively correlated with the obesity indices.

Table 5. Correlation between status of diabetes and clinical characteristics, lipid profile, and obesity variables

	Status of diabetes		Status of diabetes
		Waist circumference	0.22**
Age	0.01	Body weight	0.23**
Systolic BP	0.17**	WHR	0.15**
Diastolic BP	0.16**	Biceps SFT	0.12**
Family history	0.11**	Triceps SFT	0.13**
T-cholesterol	0.14**	Subscapular SFT	0.21**
Triglyceride	0.21**	Suprailiac SFT	0.17**
HDL-cholesterol	–0.10**	Body fat weight	0.17**
LDL-cholesterol	0.11**	Body fat %	0.09*
		BMI	0.21**

NGT (n=673), IGT (n=120), and DM (n=116) subject were included in analysis. Diabetic macrovascular risk factors including blood pressure and lipid profiles were significantly correlated with status of diabetes (** P<0.01). Family history of diabetes and all variables of obesity measurement were significantly correlated with status of diabetes (* P<0.05, ** P<0.01). BMI, body mass index; SFT, skin fold thickness; WHR, waist/hip ratio

D. Analysis of correlation among the obesity variables and the laboratory findings of metabolism

We investigated correlations between all obesity parameters and metabolic parameters to understand the influence of each obesity parameter on the various metabolic status.

The most significant and a positive associations were seen between Glucose AUC ($r=0.21$, $p<0.01$) and waist circumference, FBS, body weight ($r=0.17$, $p<0.01$), Insulin AUC, subscapular skin fold thickness ($r=0.25$, $p<0.01$), fasting insulin and BMI ($r=0.30$, $p<0.01$) (Table 6).

We revealed that all the obesity indices used in this study was significantly associated with the risk factors for diabetes macrovascular disease.

Table 6. Correlations among the lipid profiles, glucose, insulin and obesity variables

	WC	Sub	BMI	Biceps	Tri	Sup	BW	WHR	FW	F%
FBS	0.16**	0.14**	0.15**	0.05	0.04	0.07*	0.17**	0.12**	0.14**	0.09**
GAUC	0.21**	0.20**	0.19**	0.11**	0.09*	0.16**	0.20**	0.17**	0.18**	0.11**
F.Ins	0.22**	0.27**	0.30**	0.02	0.24**	0.14**	0.28**	0.09**	0.30**	0.23**
IAUC	0.20**	0.25**	0.24**	0.05	0.20**	0.20**	0.19**	0.10**	0.24**	0.23**
F.c-p	0.21**	0.20**	0.26**	0.11**	0.27**	0.19**	0.25**	0.11**	0.24**	0.17**
CAUC	0.08*	0.09**	0.11**	0.02	0.16**	0.03	0.10**	0.04	0.13**	0.14**
TC	0.18**	0.13**	0.17**	0.19**	0.06	0.06	0.17**	0.16**	0.16**	0.11**
TG	0.29**	0.28**	0.29**	0.23**	0.21**	0.21**	0.27**	0.21**	0.24**	0.15**
HDL	-0.16**	-0.23**	-0.19**	0.02	-0.22**	-0.14**	-0.19**	-0.05	-0.18**	-0.13**
LDL	0.14**	0.12**	0.14**	0.12**	0.07*	0.04	0.16**	0.11**	0.15**	0.11**

Pearson correlation was used to test the associations among the variables, *P<0.05, ** P<0.01, WC, waist circumference; Sub, subscapular; BMI, body mass index; Tri, triceps; Sup, suprailiac; BW, body weight; WHR, waist/hip ratio; FW, fat weight; F%, fat %; GAUC, IAUC and CAUC, area under the curve of glucose, insulin and c-peptide; F.Ins, fasting insulin; F.c-p, fasting c-peptide; TC, total cholesterol; TG, triglyceride

E. Comparison of obesity variables among three study groups

We further analyzed the magnitude of level of obesity by comparing various obesity indices among the three groups. As shown in table 6, we found linear relationships of obesity parameters among the three study groups, highest in DM and followed by IGT and NGT. These phenomena were observed in prepregnancy body weight, waist and hip circumference, W/H ratio, skin fold thickness, body weight, BMI, body fat weight, and body fat percent (all $p<0.05$) (Table 7).

Table 7. Comparison among the obesity variables in the three study groups

	NGT (n=673)	IGT (n=120)	DM (n=116)	P value
Prepregnancy B.Wt (kg)	59.6 ± 12.7	59.5 ± 17.9	66.6 ± 10.9	< 0.001
Waist circumference (cm)	76.2 ± 8.6	78.9 ± 9.2	81.9 ± 9.3	<0.001
Hip circumference (cm)	92.0 ± 6.7	93.0 ± 5.2	94.8 ± 7.6	<0.001
W/H ratio	0.78 ± 0.10	0.80 ± 0.09	0.82 ± 0.09	<0.001
Skin fold thickness (mm)				
Biceps	13.9 ± 5.9	15.3 ± 5.7	15.8 ± 6.9	0.001
Triceps	20.9 ± 5.8	21.5 ± 5.4	23.2 ± 6.6	<0.001
Subscapular	20.7 ± 6.4	22.0 ± 5.9	24.8 ± 6.4	<0.001
Suprailiac	21.1 ± 7.4	23.7 ± 7.1	24.6 ± 8.1	<0.001
Body weight (kg)	57.3 ± 8.8	59.1 ± 8.0	63.7 ± 10.8	<0.001
Body mass index (kg/m2)	23.0 ± 3.4	23.8 ± 3.1	25.2 ± 4.0	<0.001
Body fat weight (kg)	17.2 ± 5.3	18.0 ± 4.4	20.1 ± 6.4	<0.001
Body fat %	29.6 ± 6.0	30.1 ± 5.3	31.1 ± 5.7	<0.05

ANOVA was used to test the significance among the groups.

B.Wt, body weight ; W/H ratio, waist/hip ratio

F. Relative risk of diabetes in obesity variables

To identify the best obesity index to predict onset of DM after the GDM, we further stratified the obesity levels by the percentiles. When the level of obesity was compared between the lowest (25^{th} percentile) verse highest (75^{th} percentile) using logistic regression analysis, we found that all of the eight obesity indices were independently and significantly associated with an onset of DM during the 6 years postpartum (Table 8).

Table 8. Relative risk of diabetes in obesity variables by logistic regression between the lowest and the highest quartile

	Relative risk	95% CI
Suprailiac skin fold thickness	2.6	1.5-4.4
Triceps skin fold thickness	2.6	1.5-4.4
Waist/Hip ratio	4.4	2.5-7.6
Body fat weight	4.4	2.2-8.9
Body mass index	4.4	2.4-8.3
Subscapular skin fold thickness	4.5	2.4-8.5
Body weight	4.6	2.5-8.6
Waist circumference	5.8	2.8-11.8

For continuous variables, we stratified each variable of obesity indices according to quartiles and compared the lowest to the highest quartile. All variables were significant predictor of postpartum diabetes ($p \leq 0.001$). Waist circumference was the most significant index of diabetes (RR 5.8, 95% CI 2.8-11.8).

Of these eight significant obesity indices, we found that the waist circumference revealed with the highest relative risk (RR 5.8, 95% CI 2.8 11.8), and suprailiac and triceps skin fold thickness were the lowest relative risk (RR=2.6, 95% CI 1.5~4.4).

When the potential confounders such as blood pressure, lipid profiles, age, duration of follow-up were controlled using multiple logistic regression method, the magnitude of RR further declined (Table 9). However, waist circumference persisted as the strongest independent variable to predict postpartum DM in this study population (RR 3.86 CI 1.8-8.2). Triglyceride was positively correlated with total cholesterol but negatively with HDL-cholesterol. On the other hand, total cholesterol was positively correlated with HDL-cholesterol. Pearson correlation between triglyceride and total cholesterol was as high as 0.4. Thus, in basis of the rule of multi-colinearity, we exclude total cholesterol from the model and performed multiple logistic regression. The multiple logistic regression analysis further revealed that WC was the strongest obesity index along with the systolic blood pressure, triglyceride to be accounted as an independent risk factor to predict postpartum DM after GDM.

Table 9. Relative risk of diabetes in obesity variables after controlling for the potential confounders by using multiple logistic regression method

	Relative risk	95% CI	P value
Suprailiac skin fold thickness	2.10	1.2-3.7	<0.05
Triceps skin fold thickness	2.02	1.1-3.6	<0.05
Waist/Hip ratio	3.11	1.7-5.6	<0.001
Body fat weight	3.76	1.8-7.6	<0.001
Body mass index	3.34	1.7-6.5	<0.001
Subscapular skin fold thickness	2.82	1.4-5.6	<0.01
Body weight	3.06	1.6-6.0	0.001
Waist circumference	3.86	1.8-8.2	<0.001

Relative Risk was expressed after controlling for potential confounders such as blood pressure, lipid profiles, age, duration of follow-up.

G. Influence of waist circumference on the development of DM

Box plot graph of WC showed stepwise increment of mean value. However, NGT group included more outliers than IGT and DM groups (Fig. 5).

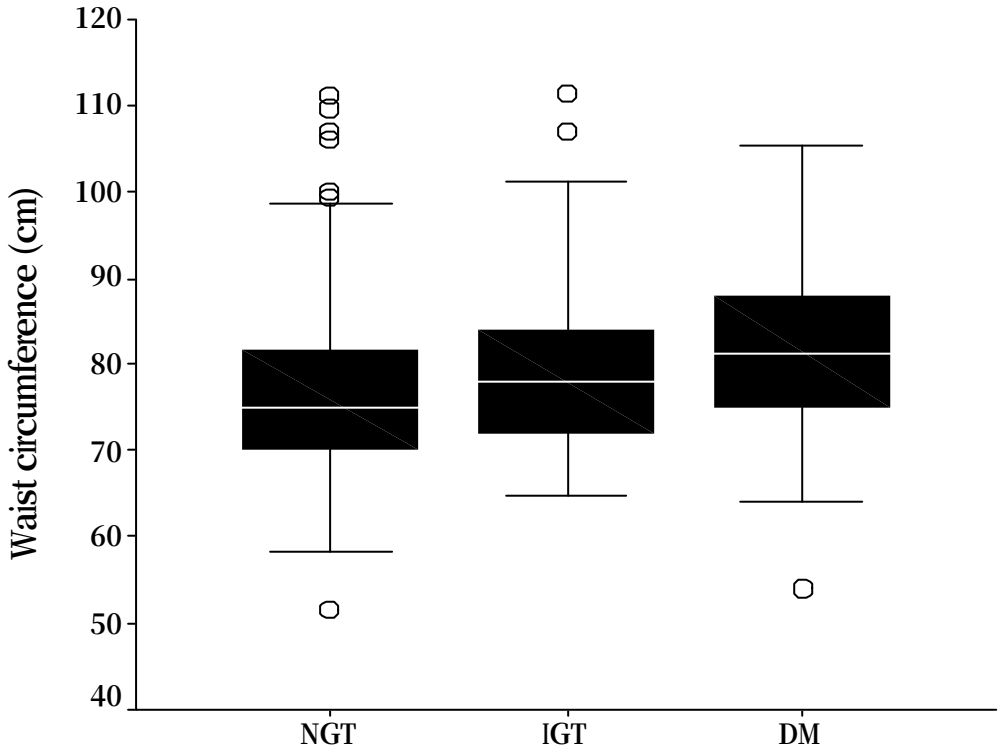


Fig. 5. Distribution of waist circumference according to the degree of glucose tolerance. Waist circumference of DM subject was significantly higher than that of NGT and IGT.

The contribution of WC for development of DM was evaluated by survival curve. Cumulative incidence (CI) of DM in obese subjects (waist circumference ≥ 80cm, CI = 62.2%) was higher than non-obese subject (waist circumference < 80cm, CI = 39.8%) by Kaplan-Meier survival analysis ($p<0.001$, Fig. 6).

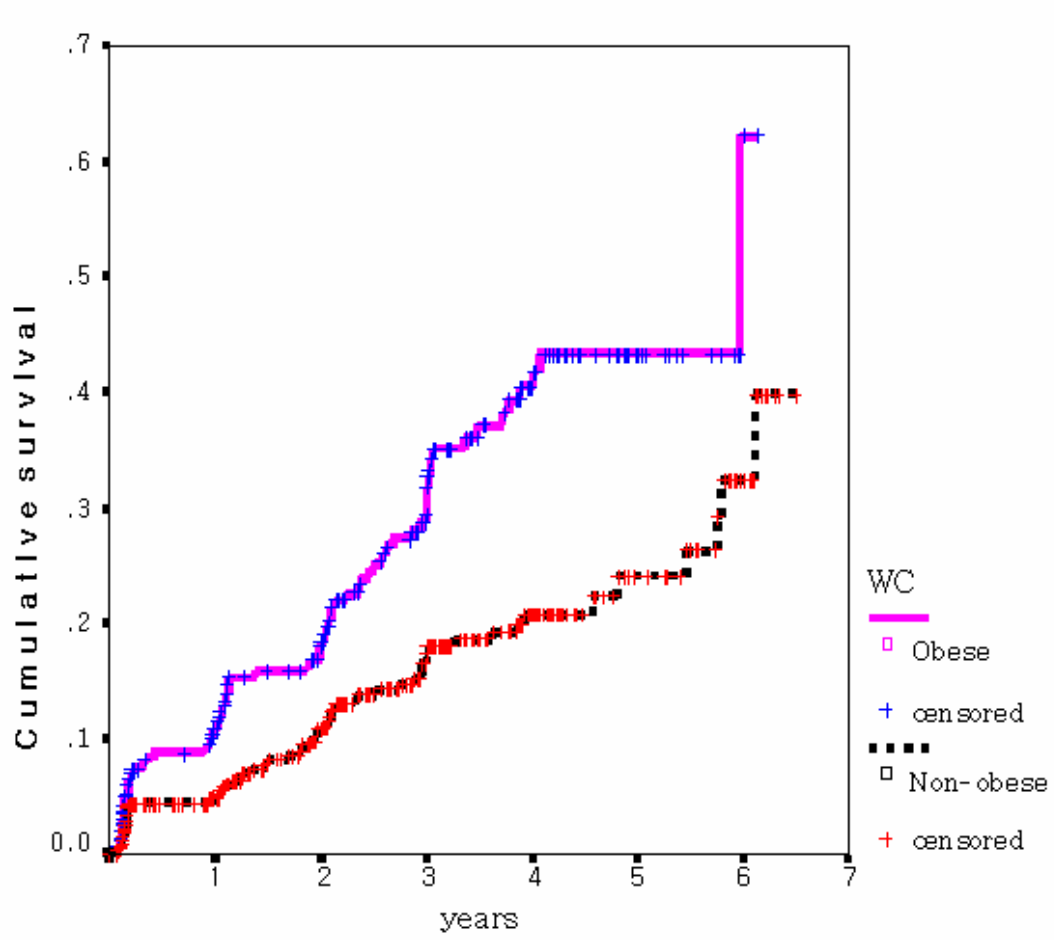


Fig. 6. Cumulative survival rate from DM according to the waist circumference. Subject group with higher waist circumference was significantly more prevalent of DM than the other group ($p< 0.0001$). 80cm of waist circumference was cut-off value of Korean obesity female. Cumulative incidences of DM was 62.2% in obese group, and 39.8% in non-obese group.

H. Macrovascular risk factor assessment

All lipid profiles except HDL-cholesterol in diabetic subject were significantly higher than either NGT or IGT subjects (Fig. 7, $p<0.01$).

Systolic and diastolic blood pressures were significantly high in DM group (Table 10, $p<0.001$).

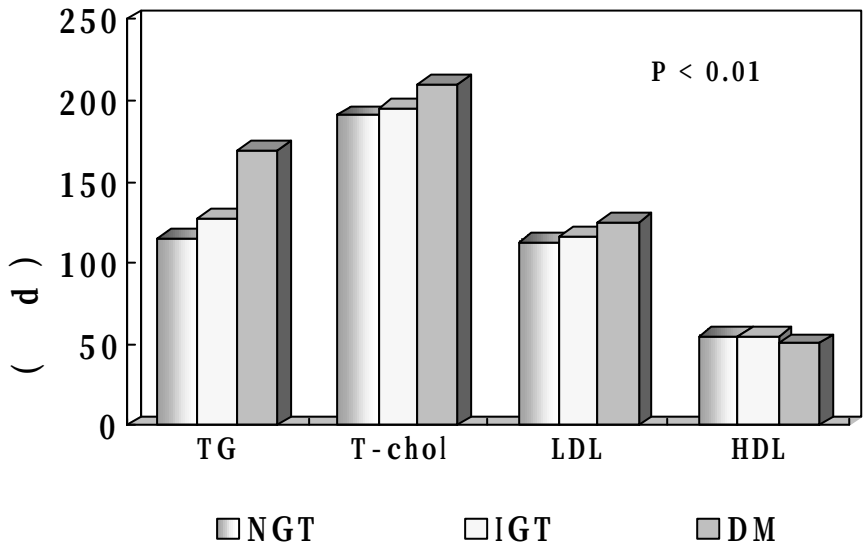


Fig. 7. Lipid profiles of the three study groups. Total cholesterol, triglyceride, and LDL-cholesterol were significantly high in diabetic group when compared to NGT and IGT ($p<0.01$). HDL-cholesterol was significantly low in diabetic group ($p<0.01$).

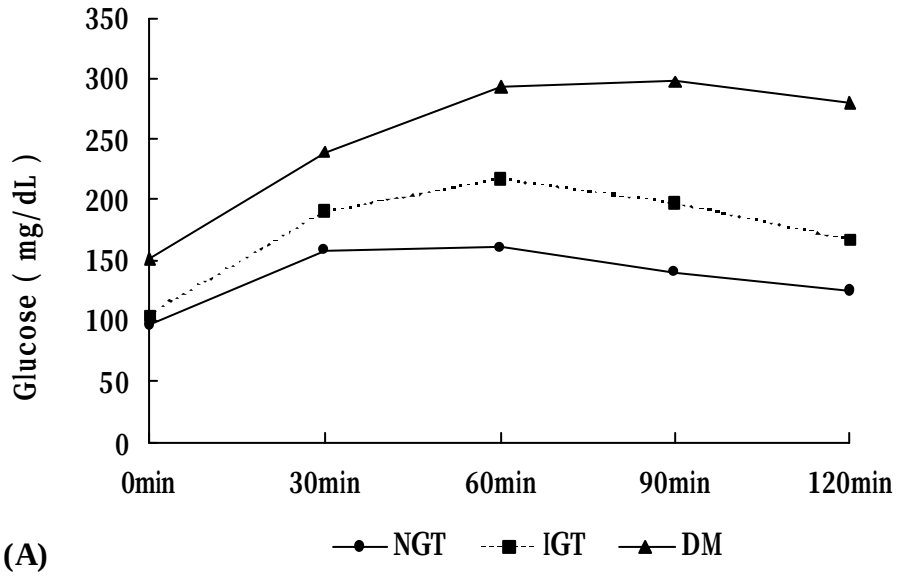
Table 10. Comparison of blood pressure between the three study groups

	NGT (n=673)	IGT (n=120)	DM (n=116)	P value
Systolic BP (mmHg)	112 ± 11	115 ± 12	117 ± 11	< 0.001
Diastolic BP (mmHg)	71 ± 9	72 ± 9	74 ± 9	< 0.001

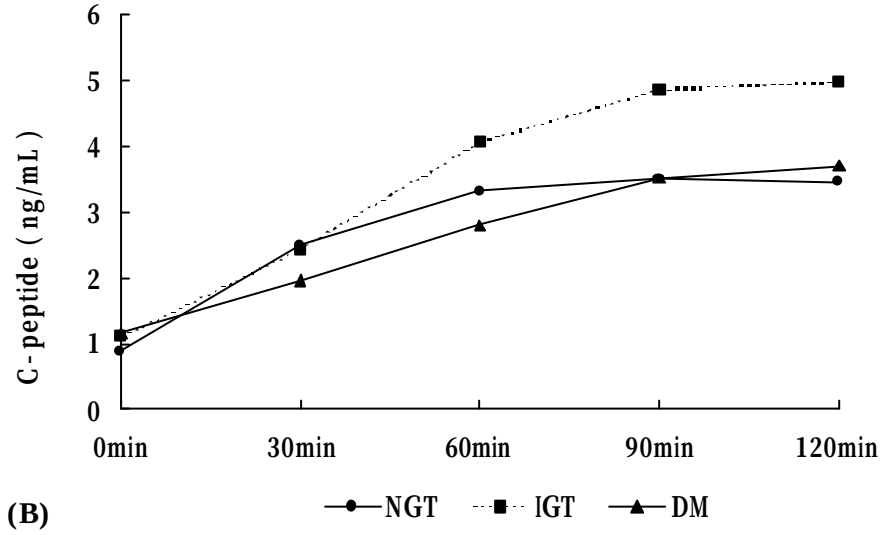
I. Glucose metabolic status assessment

1. Plasma glucose, c-peptide and insulin concentration after 75-g OGTT

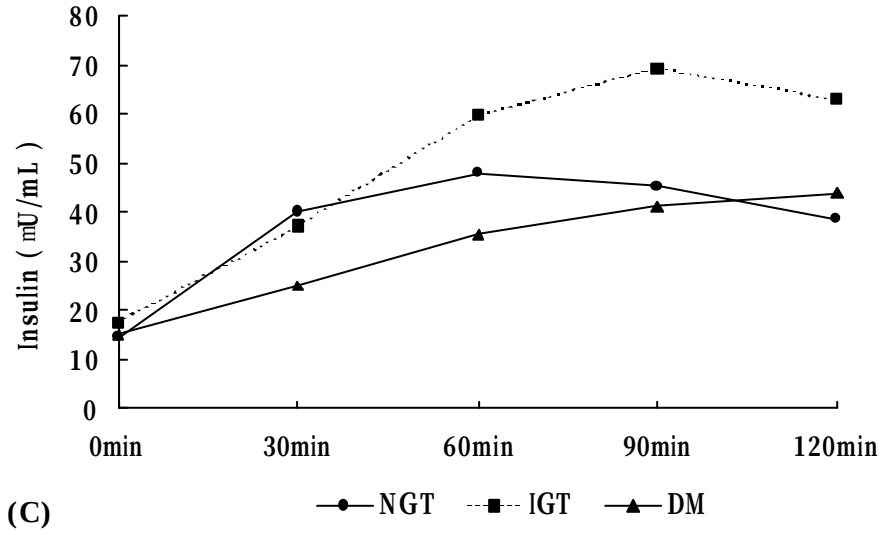
From the 75-g OGTT results, mean plasma glucose levels of DM subject at 0, 30, 60, 90 and 120 min were higher than that of NGT and DM subject ($p<0.001$, Fig. 8. A). Mean plasma c-peptide and insulin levels of IGT subject at 60, 90 and 120 min were significantly higher than that of NGT and DM group ($p<0.01$, Fig. 8. B, C).



(A)



(B)



(C)

Fig. 8. Plasma glucose, c-peptide and insulin concentration after 75-g OGTT. A, Changes of plasma glucose level. Glucose levels of DM subject were significantly higher than that of IGT and NGT subject; B, C-peptide level. C-peptide levels of IGT subject were significantly higher than that of NGT and DM subject; C, Insulin level. Insulin levels of IGT subject were significantly higher than that of NGT and DM subject.

2. Area under the curve, pancreatic beta-cell function and insulin resistance

From the 75-g OGTT results, glucose AUC (GAUC) in NGT, IGT, and DM subject were 16832 ± 3617 mg.min/dL, 22478 ± 2069 mg.min/dL, 31630 ± 8388 mg.min/dL, respectively. Insulin AUC (IAUC) in IGT subject (6208 ± 4248 ng.min/ml) were significantly higher than NGT (4584 ± 2815 ng.min/ml) and DM subject (3800 ± 2345 ng.min/ml, $p<0.001$). C-peptide AUC (CAUC) was not significantly different in NGI, IGT, and DM subject (321 ± 234 ng.min/ml, 367 ± 284 ng.min/ml, 304 ± 224 ng.min/ml, respectively). Pancreatic beta-cell function in NGT, IGT, and DM subject (2.09 ± 1.56, 2.14 ± 1.19, 1.66 ± 0.96, respectively) and insulin resistance (IR) in NGT, IGT, and DM subject (40.3 ± 26.0, 54.6 ± 67.2, 76.5 ± 63.1, respectively) were significantly different ($p<0.05$, $p<0.001$), respectively. All data from AUC, beta-cell function, and IR were expressed by log transformation for the purpose of reducing the large different scale between variables (Fig. 9).

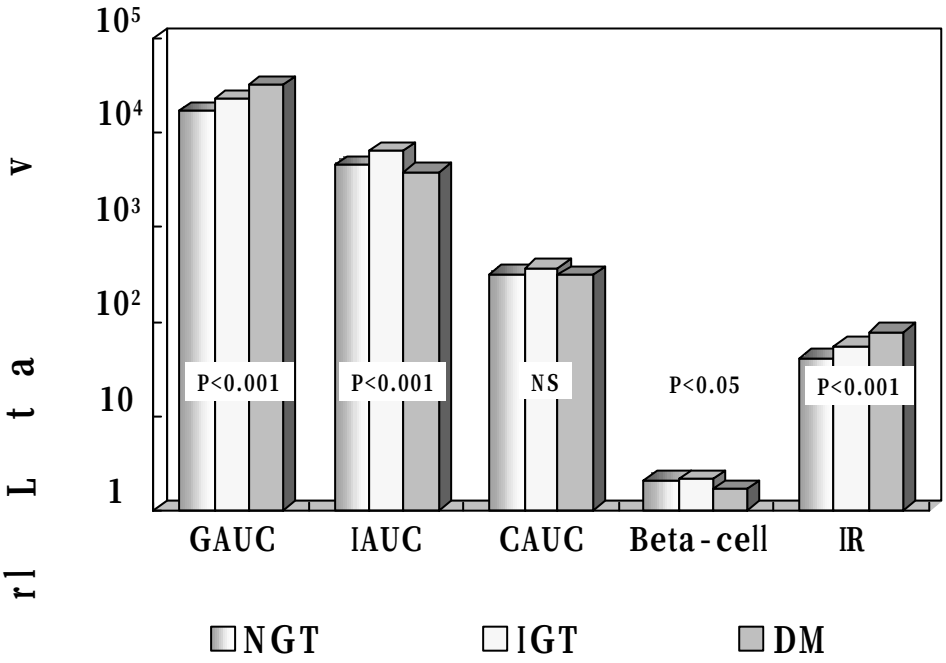


Fig. 9. Area under the curve, pancreatic beta-cell function, and insulin resistance after 75g OGTT. Results are expressed by log transformation for the purpose of reducing the large difference between variables. AUC was calculated by the trapezoidal method, and beta-cell function and insulin resistance were calculated by HOMA model. AUC of insulin and beta-cell function were significantly high in IGT group. Insulin resistance was significantly high in DM group

J. Preliminary assessment of diabetic risk factors among improved or worsened glucose tolerance subject

During follow-up periods, 14 of NGT and 16 of IGT subjects converted to DM and 46 of NGT subjects converted to IGT (W, worsened group). However, 23 of IGT and 11 of DM subjects converted to NGT and 4 of DM subjects converted to IGT (I, improved group). To determine the interventional effect of obesity indices as preventive factors of DM without intensive education, we compared the improvement of obesity indices in these two study groups. Six obesity indices such as body weight, BMI, suprailiac and subscapular skin fold thickness, hip circumference, and body fat weight accompanied with LDL-cholesterol concentration were significantly decreased in improved group more than worsened group (Table 11).

Pancreatic beta-cell function worsened in W group and IR increased more in W group than I group. However, there was no significant difference between two groups. By the Pearson correlation analysis between status of diabetes and obesity indices in improved group, body weight showed the most important interventional effect ($r=0.39$, $p<0.01$).

Table 11. Changes of blood pressure, lipid, beta-cell function, and obesity variables in improved and worsened glucose tolerance group during follow up period

	I group (n=38) *	W group (n=76) †	P value
Body weight (kg)	-2.6 ± 4.5	1.3 ± 4.3	<0.001
Body mass index (kg/m2)	-1.1 ± 1.9	0.5 ± 1.8	<0.001
Suprailiac skin fold thickness (mm)	-2.9 ± 6.8	2.4 ± 7.8	<0.01
Subscapular skin fold thickness (mm)	-1.3 ± 5.0	2.0 ± 6.5	<0.01
Hip circumference (cm)	-1.7 ± 4.4	1.3 ± 5.9	<0.01
Body fat weight (kg)	-1.8 ± 4.2	0.1 ± 3.7	<0.05
LDL-cholesterol (mg/dL)	-22 ± 29.4	-6 ± 38.7	<0.05
HDL-cholesterol (mg/dL)	3.3 ± 11.1	0.8 ± 11.5	NS
Systolic blood pressure (mmHg)	0.8 ± 8.2	2.0 ± 12.9	NS
Beta-cell function	0.07 ± 0.97	-0.16 ± 1.16	NS
Insulin resistance	1.9 ± 22.9	19.5 ± 84.3	NS

* 38 of IGT or DM women converted to NGT or IGT (I, improved group) and † 76 of NGT or IGT women converted to IGT or DM (W, worsened group) during follow up period after initial visit. Results are mean (last value - first value) ± SD. Several obesity indices accompanied with LDL-cholesterol were significantly decreased in I group.

IV. DISCUSSION

Gestational diabetes mellitus is currently defined as carbohydrate intolerance of variable severity with its first recognition during the pregnancy.[1] It has been suggested that gestational hormones are involved in metabolic changes of pregnancy, as in vitro hormones of the placental lactogen, growth hormone, and prolactin family enhances insulin production and release, as well as cell proliferation in islets of Langerhans. Simultaneously with the changes in the endocrine pancreas the sensitivity of the maternal tissues for insulin decreases during pregnancy, thereby increasing the demand for insulin.[3,4]

More than three decades ago, Wilkerson, O'Sullivan, and Mahan have initiated studies of glucose intolerance during pregnancy in an effort to identify women at risk for the subsequent development of diabetes.[18] Women with previous history of GDM were found to be at increased risk for diabetes mellitus, and various predictors were also found to be associated. Severity of glucose intolerance during pregnancy, insulin requirement during pregnancy, earlier diagnosis during pregnancy, family history of diabetes, recurrence of GDM, increasing parity, maternal age, pre-pregnancy obesity, weight gain during and after pregnancy, presence of islet cell antibodies, and delivery of a macrosomic infant were the key risk factors for DM in women with previous history of GDM.[22,28,29] However, wide geographic and ethnic variations in the incidence of abnormal glucose tolerance after GDM have been reported from the numerous studies.[30,31] In this prospective study, we observed

approximately 41% cumulative incidence rates during the 5 years postpartum period. This rate is very similar to the rate reported from Kjos et al. in the other ethnic group.[32] Although, the incidence rate of DM in Korean women with previous history of GDM was very similar, the demographic characteristics of the Korean population were considerably different. For example, most of the studies reported from Korean subjects indicated that their DM subjects were leaner than the reports based on Caucasian population.[33,34] However, despite lower level of obesity in Korean population compared to criteria of obesity, most of the obesity parameters in this study were significantly associated with an onset of DM in women with previous history of GDM. In addition to the obesity indices, most metabolic variables including hyperlipidemia and blood pressure parameters were also significantly associated with an onset of DM during the postpartum. However, the insulin changes after 75-g OGTT (IAUC) and the pancreatic beta-cell function evaluated by HOMA model during postpartum follow-up assessment were significantly lower in diabetic subjects than IGT or NGT subjects.

Obesity was considered as the high-risk factor for diabetes mellitus. Many previous studies showed that NIDDM generally started with insulin resistance and obesity before the development of overt diabetes. And the decreased pancreatic beta-cell function developed at later stage accompanied with clinical manifestations of diabetes.[35-38] DM subjects in our study showed these characteristic findings of NIDDM.

Furthermore, we found that women with a job were at increased risk for DM

during postpartum. This finding might suggest that the immobility, stress, and inadequate diet habits could be involved with an onset of DM, but further investigation are needed to confirm the cause-effect relationship. However, we also revealed that several antepartum factors, such as pre-pregnancy maternal body weight, family history, and degree of hyperglycemia during 100-g OGTT were independent predictors for an onset of NIDDM.[39,40]

A numerous epidemiological studies reported that obesity contributes to the development of type 2 diabetes mellitus after GDM.[23,24] Thus, we evaluated a various types of obesity parameters and magnitude to determine the best index to predict diabetes in Korean women with previous history of GDM. We measured body weight, BMI, waist circumference, waist hip ratio, skin fold thickness at four different sites, and percent body fat assessment by bioelectrical impedance test. Based on multiple logistic regression analysis, suprailiac and triceps skin fold thickness, waist hip ratio, percent body fat, BMI, subscapular skin fold thickness, body weight, and waist circumference were all significantly associated with a relative risk of 2.6, 2.6, 4.4, 4.4, 4.4, 4.5, 4.6, and 5.8, respectively. This relationship persisted even after adjustment of the potential confounders by using multiple logistic regression analysis. Also, we found that waist circumference persisted as the strongest independent variable to predict DM with RR of 3.86 (95% CI 1.8-8.2).

These findings suggest that GDM is characterized by insulin resistance accompanied with pancreatic beta-cell failure and central obesity represented by WC was the main pathophysiologic mechanism for development of type 2 diabetes

mellitus in Korean women with previous history of GDM.

We evaluated the improvement of obesity parameters in reversed glucose tolerant women during follow-up periods so as to assess the evidence that obesity was the key risk factor for NIDDM after GDM in natural course without intensive intervention education. 38 of IGT or DM women reversed to normal or IGT, and several variables of obesity and LDL-cholesterol were improved. In this analysis, waist circumference was more decreased in improved group than in worsened group but there was no statistical significance. This result suggests that the demographic characteristics of the subject and duration of follow-up periods included in this analysis were not fully considered.

V. CONCLUSSION

Although the absolute obesity level was not significantly high in this population, this prospective study revealed that most of the obesity parameters were also important risk factors for diabetes in Korean women with previous history of GDM. However, waist circumference was the most sensitive predictor for postpartum diabetes. Therefore, careful evaluation and monitoring of waist circumference to prevent DM in women with previous history of GDM must be considered. Furthermore, the interventional effects of waist circumference, ie. abdominal obesity, for the prevention of diabetes should be evaluated in the future.

BIBLIOGRAPHY

1. Deerochanawong C, Putiyanun C, Wongsuryrat M, Serirat S, Jinayon P: Comparison of National Diabetes Data Group and World Health Organization criteria for detecting gestational diabetes mellitus. Diabetologia 39:1070-3, 1996
2. O'Sullivan JB, Mahan CM: Criteria for the oral glucose tolerance test in pregnancy. Diabetes 13:278-85, 1964
3. Amankwah KS, Prentice RL, Fleury FJ: The incidence of gestational diabetes Obstet Gynecol 49:497-8, 1997
4. Beischer NA, Oats JN, Henry OA: Incidence and severity of gestational diabetes mellitus according to country of birth in women living in Australia. Diabetes 40(suppl 2):35-8, 1991
5. Freinkel N, Metzger BE, Phelps RL, Simpson JL, Martin AO, Radvany R, et al.: Gestational diabetes mellitus: A syndrome with phenotypic and genotypic heterogeneity. Horm Metabol Res 18:427-30, 1986
6. Agardh CD, Aberg A, Norden NE: Glucose levels and insulin secretion during a 75 g glucose challenge test in normal pregnancy. J Intern Med 240:303-9, 1996
7. Nieuwenhuizen AG, Shuiling GA, Moes H, Koiter TR: Role of increased insulin demand in the adaptation of the endocrine pancreas to pregnancy. Acta Physiol Scand 159:303-12,1997
8. Willer AK, Wagner OF, Prager R, Ulm M, Waldhausl W, Streli C, et al.: Pronounced insulin resistance and inadequate â-cell secretion characterize lean

gestaional diabetes during and after pregnancy. Diabetes Care 20:1717-23, 1997

9. Freinkel N: The Banting Lecture 1980: Of pregnancy and progeny. Diabetes 29:1023-35, 1980

10. Pederson J: Weight and length at birth of infants of diabetic mothers. Acta Endocrinol 16:330-43, 1954

11. Rizzo T, Metzger BE, Burns WJ, Burns KC: Correlations between antepartum maternal metabolism and intelligence of offspring. N Engl J Med 325:911-6, 1991

12. Smith BI, Giround CJP, Robert M, Avery ME: Insulin antagonism of cortisol action on lecithin synthesis by cultured fetal lung cells. J Pediatr87:953-5, 1975

13. Widness JA, Susa JB, Gaecia JF: Increased erythropoiesis and elevated erythropoetin in infants born to diabetic mothers and in hyperinsulinemic rhesus fetuses. J Clin Invest 67:637-42, 1981

14. Kalhan SC, Savin SM, Adam PAJ: Attenuated glucose production rare in newborn infants of insulin-dependent diabetic mothers. N Engl J Med 296:375-6, 1977

15. Pettitt DJ, Baird HR, Aleck KA: Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med 308:242-5, 1983

16. Kjos SL, Peters RK, Xiang A, Henry OA, Montoro M, Buchanan TA: Predicting future diabeted in latino women with gestational diabetes. Diabetes 44:586-91, 1995

17. National Institutes of Health: Non-insulin-dependent diabetes primary prevention trial. NIH Guide 22:1-20, 1993

18. Metzger BE, Cho NH, Roston SM, Radvany R: Prepregnancy weight and ntepartum insulin secretion predict glucose tolerance five years after gestational diabetes mellitus. Diabetes care 16:1598-605, 1993

19. Damm P: Diabetes following gestational diabetes mellitus. In Diabetes and Pregnancy (ed. Dornhorst A, Hadden DR) Chichester, U.K., Wiley, 1996, pp. 341-50

20. Steinhart JR, Sugarman JR, Connell FA: Gestational diabetes is a herald of NIDDM in Navaji women. Diabetes Care 20:943-7, 1997

21. Ali Z, Alexis S: Occurrence of diabetes mellitus after gestational diabetes mellitus I Trindad. Diabetes Care 13:527-9, 1990

22. Pallardo F, Martin-Vaquero P, Herranz L, Janez M, Garcia-Ingelmo T, Gonzalez A, et al.: Early postpartum metabolic assessment in women with prior gestational diabetes. Diabetes Care 22:1053-8, 1999

23. George AB, Henry AJ, Ethan AHS: Evaluation of the Obese patient. JAMA 235:1487-91, 1976

24. Wein P, Dong ZG, Beischer NA, Sheedy MT: Factors predictive of recurrent gestational diabetes diagnosed before 24 weeks' gestation. Am J Perinatol 12:352-6, 1995

25. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039, 1979

26. Friedwald, WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative

ultracentrifuge. Clin. Chem 18:499 -502, 1972

27. Williams, D P, Going SB , Lohman TG, Hewitt MJ, Haber AE: Estimation of body fat from skinfold thicknesses in middle-aged and older men and women: a multiple component approach. Am J Hum Biol 4:595-605, 1992
28. Lavin JP Jr: Screening of high-risk and general populations for gestational diabetes. Clinical application and cost analysis. Diabetes 34 Suppl 2:24-7, 1985
29. Spong CY, Guillermo L, Kuboshige J, Cabalum T: Recurrence of gestational diabetes mellitus: identification of risk factors. Am J Perinatol 15:29-33, 1998
30. Dooley SL, Metzger BE, Cho NH: Gestational diabetes mellitus. Influence of race on disease prevalence and perinatal outcome in a U.S. population. Diabetes 40 Suppl 2:25-9, 1991
31. Green JR, Pawson IG, Schumacher LB, perry J, kretchmer N: Glucose tolerance in pregnancy: ethnic variation and influence of body habitus. AM J Obstet Gynecol 163:86-92, 1990
32. Kjos S, Buchanan T, Peters R: Postpartum glucose tolerance testing identifies women with recent gestational diabetes who are at highest risk for developing diabetes within five years. Diabetes, suppl 43:136A, 1994
33. Jang HC, Cho NH, Jung KB, Oh KS, Dooley SL, Metzger BE: Screening for gestational diabetes mellitus in Korea. Int J Gynaecol Obstet 51:115-22, 1995
34. Ramachandran A, Snehaltha C, Viswanathan V, Viswanathan M, Haffner SM: Risk of noninsulin dependent diabetes mellitus conferred by obesity and central aadiposity in different ethnic groups: a comparative analysis between Asian

Indian, Mexican American and Whites. Diabetes Res Clin Pract 36:121-5, 1997

35. Saad MF, Knower WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH: A two-tep model for development of non-insulin-dependent diabetes. Am J Med 90:229-35, 1991

36. DeFronzo RA, Bonadonna RC, Ferrannini E: The pathogenesis of NIDDM: a balanced overview. Diabetes Care 15:318-68,1992

37. Martin BC, Warram JH, Krolweski AS, Bergman RN, Soeldner JS, Kahn CR: Role of glucose and insulin resistance in the development of type 2 diabetes mellitus: results of a 25-year follow-up study. Lancet 340:925-9, 1992

38. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, et al: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. N Engl J Med 329:1988-92, 1992

39. El Mallah KO, Narchi H, Kulaylat NA, Shaban MS: Gestational and pre-gestational diabetes: comparison of maternal and fetal characteristics and outcome. Int J Gynaecol Obstet 58:203-9, 1997

40. Kjos SL, Peters RK, Xiang A, Henry OA, Montoro M, Buchanan TA: Predicting future diabetes in Latino women with gestational diabetes. Diabetes 44:586-91, 1995

- 국문요약 -

임신성 당뇨병의 과거력이 있는 여성에서 산후 현성 당뇨병 발병의 주요 위험 요소로 작용하는 허리둘레의 중요성

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목적: 임신성 당뇨병의 과거력이 있는 많은 여성들은 산후 추적 관찰 기간중 일부는 인슐린의존형 당뇨병으로 대부분은 인슐린비의존형 당뇨병으로 전환된다. 산후 현성 당뇨병의 발병과 관련되어 비만, 당뇨병 가족력, 임신전 산모의 체중, 산모의 고령, 출산력, 임신성 당뇨병의 과거력 등의 몇가지 요소들은 이미 알려진 상태이다. 산후 인슐린비의존형 당뇨병의 위험요소중에서 비만에 대한 측정 지표들은 매우 다양하다. 따라서 본 연구에서는 임신성 당뇨병의 과거력이 있는 한국 여성에서 비만 측정 지표들과 인슐린비의존형 당뇨병 발병과의 연관성을 조사하고자 한다.

대상 및 방법: 임신성 당뇨병의 과거력이 있는 909 명의 여성을 대상으로 산후 약 6년 이상의 기간에 걸쳐 매년 추적 검사를 하였다. 출산후 최초의 방문은 산후 6주째로 하였고 이후 매년 추적 검사를 실시하였다. 임신성 당뇨병으로 진단 받은 시기에 환자들의 임신전 체중, 출산력, 활동량,

식습관 등을 포함한 임신전 특성들과 가족력 등을 조사하였고, 임신성 당뇨병 진단 당시의 100-g 경구당부하 검사 결과들을 비교분석 하였다. 출산후 추적 관찰 시기에는 75-g 2시간 경구당부하 검사를 실시하여 공복, 포도당 투여후 30분, 60분, 90분, 120분째 혈중 포도당 농도, 인슐린 농도, c-peptide 농도를 측정하고 공복 지질농도, 생활습관 분석, 식사 평가와 함께 체중, 체질량지수, 허리와 엉덩이 둘레, 피하지방 두께, 체지방 측정기를 이용하여 체지방비와 지방질량 등을 포함한 비만 측정 표지자들에 대한 검사를 실시하였다.

결과: 총 909 명의 임신성 당뇨병의 과거력이 있는 대상군 중에서 6 년 이상의 추적 기간중 12.8%에 해당하는 116 명의 여성이 산후 현성 당뇨병으로 전환 되었다. 산후 정상 혈당을 유지하는 군, 당불내인성군, 당뇨로 전환된 군을 비교했을 때 세군의 평균 연령 및 출산력에는 유의한 차이가 없었고 가족력은 당뇨군에서 55.2%로 당불내인성군과 정상군에 비해 유의하게 높은 결과를 보여주었으며 특히 세군 모두에서 부모의 당뇨병력이 70% 이상으로 높게 나타났다. 임신성 당뇨병 진단당시 실시한 100-g 경구당부하 검사 결과는 정상군, 당불내인성군, 당뇨군의 순으로 당뇨군에서 유의하게 높았다 ($p<0.001$). 모든 비만 표지자들은 정상군에 비해 당불내인성군, 당뇨군의 순으로 당뇨군에서 유의하게 높게 측정되었다 ($p<0.001$). 당뇨병 발생과 비만도의 상관관계 분석에서 허리둘레, 견갑하 피하지방 두께, 체지방 질량, 체질량지수 등의 변수가 혈중 포도당 농도와 유의한 관계를 보였지만 ($r=0.21$, 0.20, 0.20, 0.19, respectively), 이중 가장 유의한 관계를 보이는 비만 변수는 허리둘레

였다 (r=0.21, p<0.01). 비만 측정 변수들이 당뇨병 발생에 미치는 영향을 보다 자세히 분석하기 위해 각 변수들을 백분율로 나누어 상위 25%와 하위 25%의 대상군을 회귀분석에 의해 비교한 결과 8 개의 유의한 비만 변수들 중에서 허리둘레가 가장 높은 비교위험도를 보이는 변수로 나타났다 (RR=5.8, 95% CI 2.8 11.8). 비만 측정변수와 함께 당뇨병 발생의 동반 위험요소로 작용하는 혈압, 혈중 지질농도, 연령, 추적 기간 등의 독립변수를 교정한 뒤 회귀분석한 결과 허리둘레의 비교위험도는 여전히 3.86 의 높은 결과를 보였다 (95% CI 1.8~8.2).

추적 기간중 14 명의 정상군과 16 명의 당불내인성군이 당뇨군으로, 46 명의 정상군이 당불내인성군으로 전환되었고 (W, 악화군), 23 명의 당불내인성군과 11 명의 당뇨군이 정상군으로, 4 명의 당뇨군이 당불내인성군으로 각각 전환되었다 (I, 호전군). 이 두군을 비교한 결과 체중, 체질량지수, 장골 상부 피하지방 두께, 견갑하 피하지방 두께, 엉덩이 둘레, 체지방 질량 등의 6 가지 비만 측정 변수들과 함께 저밀도콜레스테롤 농도가 악화군보다 호전군에서 유의하게 감소하였다

결론: 임신성 당뇨병의 과거력이 있는 한국 여성을 대상으로 한 전향적 연구에서 비만 측정 변수들을 포함한 많은 변수들이 산후 당뇨병 발병의 예측인자로 나타났으며, 특히 비만 변수들 중 허리둘레는 가장 중요한 독립 위험 요소로 작용한다는 것을 알 수 있었다. 잎으로 이러한 비만 측정 변수를 교정할 수 있는 식사요법, 운동요법, 행동수정요법 등을 이용한 당뇨병 발병의 예방적 접근에 대한 연구가 필요할 것으로 생각된다.

핵심되는 말: 정상내당능, 당불내인성, 인슐린비의존형 당뇨병, 임신성 당뇨병

Appendix 1. Sequential examination flow sheet of the follow-up