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Clinical Symptoms Used for Screening Diabetic Populations with Family History of Type 2 Diabetes Mellitus

Siti Marlina[1], I Dewa Putu Pramantara[2], Hari Kusnanto[3], Mark Alan Graber[4]

[1] *Puskesmas* Kasihan I (Community and Primary Health Care Center); Bantul; Yogyakarta; Indonesia
[2] Department of Internal Medicine – Geriatric Division; Sardjito Hospital; Yogyakarta; Indonesia
[3] Department of Family and Community Medicine; Faculty of Medicine, Public Health, and Nursing; Universitas Gadjah Mada; Indonesia
[4] Department of Family Medicine; University of Iowa; United State of America

Corresponding Author:
Siti Marlina: Puskesmas Kasihan 1, Jl. Bibis km 8, Bangunjiwo, Kasihan, Bantul, Yogyakarta - 55184, Indonesia
Email: sitimarlina78@gmail.com

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ABSTRACT:
Background: The annual prevalence of diabetes is increasing worldwide. With this growing concern, the identification of clinical symptoms in high risk populations, such as those with a family history of diabetes, is becoming increasingly important. **Objectives:** This study aimed to determine the use of clinical symptoms and history as a screening tool for diabetes mellitus (DM) in a population with a family history of Type 2 Diabetes Mellitus (T2DM). **Methods:** The design of this research was a cross sectional study. The subjects of this study were a sample population with family history of T2DM living in Kasihan and Sewon District of Bantul Regency. Data were collected through interviews with questionnaires, anthropometric measurements, total cholesterol tests, triglycerides and fasting blood glucose tests. Data analysis used univariate, bivariate and multivariate analyses. For screening purposes, validity was performed againstrisk factors with fasting blood glucose as a gold standard. **Results:** Prevalence of DM was 30.5%, and prediabetes 26.5%. Body Mass Index (BMI) prevalence ≥23 kg/m^2 59.02%, hypertension 42.62%, physical inactivity 21.31%, and dyslipidemia 78.69%. Polyuria, polydipsia, and weight loss were significantly associated with T2DM. Birth history of weight ≥4 kg or Gestational Diabetes Mellitus (GDM) was a risk factor associated with T2DM incidence (p = 0.018; OR: 1.93; CI 95%: 1.12-3.34). The sensitivity of a combination of several factors, birth history of baby ≥4 kg or GDM with dyslipidemia (sensitivity 87.3% specificity 40.9%), birth historyof weight ≥4 kg or GDM with dyslipidemia and hypertension (sensitivity 94.7% specificity 26.7%), combination of the five factors studied (sensitivity 92.3% specificity 50%). Combination of birth history of heavy baby ≥4kg or GDM and BMI ≥ 23 kg/m^2 and hypertension had a likelihood ratio of 9. **Conclusions:** This study determined the prevalence of T2DM in populations with a family history of diabetes is high, with birth history of weight ≥ 4 kg or GDM as a factor associated with T2DM, and other clinical symptoms having a fairlyhigh prevalence. Therefore, a comprehensive lifestyle change needs to be done.

Keywords: *diabetes mellitus, family history of DM, screening, risk factors, T2DM incidence.*

BACKGROUND

The World Health Organization (WHO) predicts an increase in the number of people with diabetes mellitus (DM) in Indonesia from 8.4 million in 2000 to 21.3 million in 2030[1]. While the annual prevalence of undiagnosed DM in Indonesia is approximately 4.1% with a 5.6% prevalence for diabetes[2]. The highest prevalence of diabetes in Indonesia was found in Yogyakarta regency (2.6%). About 25% of newly diagnosed T2DM patients have diabetic retinopathy or microalbuminuria. About one-third of people with diabetes do not know they have T2DM, and the time-span between onset and diagnosis is on average 7 years[3,4].

More than 95% of the population of DM is Diabetes Mellitus Type 2 (T2DM). As a result of gene-environment interactions with several risk factors such as age, sex, family history, obesity and hypertension, one of the strategies of diabetes prevention and earlier diagnosis is screening in high risk groups. Family history is one of the most decisive factors of T2DM[5]. Recent research

shows that having parents with T2DM will increase the children's risk of developing diabetes 2-4 times. Also, the relationship between siblings having diabetes is stronger than that between parents and children[6]. The identification of clinical symptoms in a population with a family history of diabetes associated with increased susceptibility to diabetes development is becoming increasingly important. This study aimed to determine the clinical symptoms and other factors which can be used as a screening tool in a population with a family history of diabetes who have not been diagnosed yet with T2DM.

RESEARCH METHODS

The design of this research was a cross sectional study. The subjects of this study were a sample population with family history of T2DM living in Kasihan and Sewon District of Bantul Regency. Sample selection method was purposive sampling. The number of research subjects was 200. The inclusion and exclusion criteria are presented in Table 1:

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Have a history of children, parents, siblings or women who have diabetes mellitus	1. Have CVD or stroke
2. Male or female over the age of 40 years.	2. Pregnant women.
3. Have never been diagnosed DM by anamnesis	
4. Willing to follow the research by signing informed consent.	

Data were collected through interviews with questionnaires asking about age, sex, history of taking antihypertensive drugs, lipid-lowering drugs, and birth history of infants with weight ≥ 4 kg and or GDM, then anthropometric and total cholesterol, triglyceride and fasting blood glucose measurements. Subjects were considered to have undiagnosed T2DM if the fasting blood glucose ≥ 126 mg / dl, prediabetes if fasting blood glucose levels 100 - 125 mg / dl. Data analysis used univariate, bivariate and multivariate analyses. For screening purposes validity was performed against risk factors with fasting blood glucose as a gold standard. Data analysis used STATA 12 program.

RESULTS

From a total of 200 study subjects with a family history of T2DM, the patient characteristics were listed in Table 2.

Table 2. Research subject characteristics

Subject characteristic		Amount (n)	Percentage (%)
Gender	Men	61	30.5
	Women	139	68.5
Relationship with the Person with DM	Parents	25	12.5
	Child	111	55.5
	Siblings	64	32
Age	40 – 49	113	56.5
	50 – 59	50	25
	60 – 69	26	13
	70 – 79	8	4
	> 80	3	1.5

Our study population had more female research subjects, which was 68.5% compared to men 30.5%. Most subjects were aged 40-59 years (56.5%), and the relationship of most subjects with the diabetic patients were as their children, and the parents with T2DM were (55.5%).

Based on blood glucose, participants were categorized as either non-diabetic, pre-diabetic or diabetic. The association of subjects diagnosed as diabetics based on the classification of diabetes can be seen in Table 3. In this study pre-diabetic and T2DM patients were found from subjects who had diabetic parents.

Table 3. The association of subjects with Diabetics based on the classification of diabetes

The association of subjects with Diabetics	Prediabetes N (%)	Diabetes Mellitus n (%)
Parents	3 (5.67)	9 (14.75)
Child	32 (60.37)	31 (50.82)
Siblings	18 (33.96)	21 (34.43)
Total	53 (100)	61 (100)

Characteristics of study subjects diagnosed with diabetes based on risk factors of birth history weight ≥ 4 kg or GDM, BMI ≥ 23 kg/m^2, hypertension, dyslipidemia, and physical inactivity can be seen in the Table 4.

The percentage of subjects with a history of having a weight ≥ 4 kg or GDM was 13.04%, while 65% had a Body Mass Index (BMI) ≥ 23. Thirty-six and one-half percent (36.5%) of the subjects were hypertensive, 68% had dyslipidemia while 16% were physically inactive.

Based on bivariate analysis, several statistically significant variables were associated with T2DM with p <0.05 including dyslipidemia. Birth history of weight ≥ 4 kg or GDM had p = 0.059; with RP 1.75 CI 95% 1.04 – 2.93. The bivariate analysis performed on all subjects not

Table 4. Characteristics of study subjects diagnosed with Diabetes based on risk factors

Risk factor		Amount (n)	Percentage (%)
Birth History Weight ≥ 4 kg or Gestational Diabetes Mellitus	Yes	18	13.04
	No	121	86.96
Body Mass Index ≥ 23 kg/m^3	Yes	130	65
	No	70	35
Hypertension	Yes	73	36.5
	No	127	63.5
Dyslipidemia	Yes	136	68
	No	64	32
Physical Inactivity	Yes	32	16
	No	168	84

distinguished by gender can be seen in Table 5.

Multivariate analysis of logistic regression in Table 6 displays the results of a birth history of ≥ 4 kg or a history of GDM as an independent risk factor for development of diabetes with RR 1,93 (CI 95%:1.12 – 3,34). Those aged 70-79 years had a risk 2.21 times of becoming diabetic RR 2.21 (CI 95%:1.10 – 4.43). Being female and ages of 50-59 years were confounding factors.

Table 5. Bivariate analysis result of risk factor with T2DM diagnosed

DM risk factors		Diabetes Mellitus Yes n	Yes %	No n	No %	*p* value	RP	Confidence interval 95%
1. Birth History ≥ 4 kg / Gestational Diabetes Mellitus	Yes	9	14.75	9	6.47	0.059	1.75	1.04 – 2.93
	No	52	85.25	130	93.53			
2. Body Mass Index ≥ 23 kg/m^3	Yes	36	59.02	94	67.63	0.239	0.77	0.50 – 1.17
	No	25	40.98	45	32.37			
3. Hypertension	Yes	26	42.62	47	33.81	0.233	1.29	0.85 – 1.96
	No	35	57.38	92	66.19			
4. Dyslipidemia	Yes	48	78.69	88	63.31	0.031	1.73	1.01 – 2.96
	No	13	21.31	51	36.69			
5. Physical Inactivity	Yes	13	21.31	19	13.67	0.174	1.21	0.87 – 2.30
	No	48	78.69	120	86.33			

Table 6. Multivariate analysis of logistic of DM risk with age and gender adjustment

Variable	*p* value	RR	Confidential interval (CI 95%)
Men	0.254	0.42	0.75 – 1.94
Age Category			
40 – 49	0.884	0.95	0.48 – 1.86
60 - 69	0.855	0.93	0.46 – 1.89
70 - 79	0.024	2.21	1.10 – 4.43
80 +	0.878	1.10	0.29 – 4.13
Birth History ≥ 4 kg / Gestational Diabetes Mellitus	0.018	1.93	1.12 – 3.34
Body Mass Index ≥ 23 kg/m^3	0.53	0.86	0.55 – 1.34
Hypertension	0.911	1.26	0.65 – 1.61
Dyslipidemia	0.128	1.53	0.88 – 2.67
Physical Inactivity	0.419	1.24	0.73 – 2.10

As shown in Table 7 below, the classical symptoms of T2DM, polyuria, polydipsia, and weight loss were significantly statistically associated with T2DM.

Sensitivity of each birth history of weight ≥ 4 kg or GDM, BMI ≥ 23kg/m^2, hypertension, dyslipidemia, and physical inactivity was quite low, as shown in Table 8.

The sensitivity for detecting diabetes changed after analysis

Table 7. Bivariate analysis of DM classical symptoms with T2DM incidence

Classical symptoms		Diabetes Mellitus Yes n	Yes %	No n	No %	*p* value	RP or RR	*Confidence interval* 95%
Polyuria	Yes	19	43.18	25	17.99	0.039	1.06	1.04-2.45
	No	42	68.85	114	82.01			
Polydipsia	Yes	25	42.62	33	27.74	0.007	1.77	1.18-2.66
	No	35	57.38	106	76.26			
Polyphagia	Yes	13	21.13	35	25.18	0.555	0.85	0.05-1.44
	No	48	78.69	104	74.82			
Weight loss	Yes	11	18.03	7	5.04	0.003	2.22	1.43-3.44
	No	50	81.97	132	94.96			

Table 8. Validity test results of risk factors with GDP as a gold standard

Risk factors	Sensitivity (%)	Specificity (%)	PPV	NPV	ROC	OR	LR(+)	LR(-)
1. Birth History ≥ 4 kg / Diabetes Mellitus Gestational	22.5	90.9	6.2	97.8	0.567	2.9	2.48	0.853
2. Body Mass Index ≥ 23 kg/m^3	59	32.4	2.28	96.7	0.457	0.689	0.873	1.27
3. Hypertension	42.6	66.2	3.26	97.7	0.544	1.45	1.26	0.867
4. Dyslipidemia	36.7	78.7	4.39	97.9	0.577	2.14	1.72	0.805
5. Physical Inactivity	21.3	86.3	4	97.6	0.538	1.71	1.56	0.911

of a combination of several risk factors. Combination of birth history of weight ≥ 4 kg or gestational diabetes mellitus with dyslipidemia (sensitivity 87.3% specificity 40.9% PPV 3.79% NPV 99.2% ROC 0.641 and OR 4.75). Combination of birth history of weight ≥ 4 kg or gestational diabetes mellitus with dyslipidemia and hypertension (sensitivity 94.7% specificity 26.7% PPV 3.33% NPV 99.5% ROC 0.607 OR 6.55). The combination of all five risk factors was 92.3% sensitive, specificity 50%, PPV 4.7% NPV 99.6% ROC 0.712 and OR 12. The three combinations were only in female subjects as shown in Table 9.

Combination of birth history of heavy infant ≥ 4kg or Gestational Diabetes Mellitus (GDM) and BMI ≥ 23 kg/ m^2 and hypertension had likelihood ratio of 9. In men the combined sensitivity of several risk factors was low (Table 10). The combination of IMT and dyslipidemia had a sensitivity of 63.6% with ROC 0.612.

Table 9. Validity Test Result of Risk Factors with GDP as a Gold Standard for Women

Risk factors	Sensitivity (%)	Specificity (%)	PPV	NPV	ROC	OR	LR(+)	LR(-)
1. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & IMT	42.9	78.9	5.15	98.1	0.609	2.81	2.04	0.724
2. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & Dyslipidemia	87.3	40.9	3.79	99.2	0.641	4.75	1.48	0.311
3. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & Physical Inactivity	3.57	100	100	97.5	0.518	∞	∞	0.964
4. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & Hypertension	18.2	96.8	13.3	97.8	0.575	6.78	5.73	0.845
5. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & IMT & Hypertension	42.6	95.2	19.4	98.4	0.69	15	9	0.6
6. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & IMT & Dyslipidemia	76.9	54.5	4.32	98.9	0.657	4	1.69	0.423
7. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & Dyslipidemia &Hypertension	94,7	26,7	3,33	99,5	0,607	6,55	1,29	0,197
8. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & Dyslipidemia & Physical Inactivity	100	8.33	2.83	100	0.542	∞	1.09	0
9. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & Physical Inactivity & Hypertension	5.88	100	100	97.5	0.529	∞	∞	0.941
10. Birth History ≥ 4 kg / Diabetes Mellitus Gestational & Physical Inactivity & Hypertension & Dyslipidemia	92.3	50	4.7	99.6	0.712	12	1.85	0.154

Table 10. Validity test result of combination between risk factors with GDP as a gold standard for men

Risk factors	Sensitivity (%)	Specificity (%)	PPV	NPV	ROC	OR	LR(+)	LR(-)
1. IMT & Hypertension	56.3	58.3	3.48	98	0.573	1.8	1.35	0.75
2. IMT & Dyslipidemia	63.6	58.8	3.96	98.4	0.612	2.5	1.55	0.618
3. Hypertension & Dyslipidemia	61.5	30.4	2.31	96.7	0.460	0.7	0.885	1.26
4. Hypertension & Physical Inactivity	65.4	25	2.27	96.4	0.452	0.63	0.872	1.38
5. Physical Inactivity & Dyslipidemia	71.4	32.1	2.73	97.7	0.518	1.18	1.05	0.889
6. IMT & Hypertension & Dyslipidemia & Physical Inactivity	66.7	20	2.18	95.7	0.433	0.5	0.833	1.67

DISCUSSION

Family disease history as a predictor of disease development can be useful in helping to determine who to screen for a disease. The use of family history in diabetic patients can be helpful base on an indication of at least 50% of the probability of developing T2DM in individuals at risk[5]. In this study the prevalence of diabetes was 30.5% and 26.5% were considered prediabetes. This prevalence is much higher than the prevalence of undiagnosed diabetes in the general population in Indonesia (4.1%)[2]. Up to 70% of individuals with prediabetes will develop diabetes. Several studies have shown a reduced risk of developing diabetes among those with prediabetes after lifestyle and pharmacological interventions[7]. The prevalence of diabetes in the children of diabetic parents was 50.82%. The risk of a child getting diabetes is greater if one of his/her parents has diabetes[2].

The association of BMI ≥ 23 kg/m^3 with T2DM was not statistically significant. In this study the BMI analyzed was not differentiated between overweight and obesity, but BMI ≥ 23 kg / m^2 could include both criteria. This is supported by a similar study by Trisnawati[8] in Bali where obesity based on IMT did not increase the incidence of T2DM.

The prevalence of dyslipidemia in T2DM diagnosed subjects in this study was 78.69%. The results of bivariate analysis of dyslipidemia with T2DM incidence were statistically significant. These results were in line with the study of Mihardja et al[9] which examined the prevalence and clinical profile of diabetes mellitus in the urban productive age community in Indonesia, the prevalence of dyslipidemia by more than 50% among newly diagnosed T2DM and T2DM subjects. Improved lipid profile in people with diabetes with lifestyle modification focused on reducing saturated fat intake, cholesterol intake, fiber increase, weight loss, increased physical activity[7]. Regular lipid profile monitoring performed in primary care plays an important role in detecting lipid disorders and managing dyslipidemia in both diabetic and nondiabetic patients. Lipid profile examination is an examination that has been common in primary care.

The prevalence of hypertension in this research was quite high, which was 42.62%, although statistically it did not show a correlation of hypertension with T2DM incidence. This prevalence was higher than that of Amini and Janghorbani[10] whereas the prevalence of systolic hypertension was 19.1% and diastolic 15.7% in subjects with a family history of T2DM. In T2DM, the prevalence of hypertension is quite high at the time of T2DM diagnosis. This pattern is probably due to the presence of essential hypertension and its association with obesity[11].

Physical activity with T2DM incidence was not statistically significant. The results of this study were similar to those of Raghupathy et al.[12] where physical inactivity was unrelated to T2DM incidence. The study was conducted in the Vellore region, India which was a rural area. Subjects who lived in rural areas have more physical activity. There was similarity of area with this research for sampling which was in a rural area. Physical activity for 7 days was asked using questionnaires so there was a possibility that the data given was not in accordance with the actual condition due to incorrect memory or misunderstanding.

In the multivariate logistic regression analysis, dyslipidemia was not an independent risk factor. After adjustment for age and sex, independent risk factors associated with T2DM incidence were a history of having a baby ≥ 4 kg or a history of gestational diabetes mellitus. And the confounding factor was women and age 50-59 years. After adjustment according to age and sex RR increased from 1.75 to 1.93. The influence of confounding factors can enlarge or minimize the actual relationship. In this study women and 50-59 years of age increased the risk factor of birth history of heavy babies ≥ 4 kg or GDM against the incidence of diabetes. Women and 50-59 years of age could be a risk factor for the incidence of diabetes.

This result was similar to the Eriksson[5] study, which found gestational diabetes mellitus after 15 years followed by incidence of T2DM by 35-40% or 3-5% per year. GDM was not only associated with an increased risk of T2DM in the mother but also an increased risk of T2DM in offspring. Diabetic screening for pregnant women who visited the health service was performed, especially those with risk factors. For pregnant women who have not been diagnosed with diabetes they were screened for gestational diabetes mellitus at gestational age 24-28 weeks. Then if the woman is suffering from GDM then after 6-12 weeks post-partum they need to be re-screened for persistent diabetes. Women

with a history of having a baby ≥ 4 kg or GDM should be screened for at least once every 3 years. If women with a history of GDM in the prediabetes phase, lifestyle changes or metformin interventions need to be done to prevent the occurrence of diabetes[12].

The prevalence of classical diabetes symptoms such as polyuria, polydipsia, polyphagia, and weight loss respectively were 43.18%; 42.62%; 21.13%; and 18.03%. This result was higher than the prevalence of classical symptoms studied by Habtewold et al.[13] in Ethiopia, where the prevalence of polydipsia was 13.3%; 14.5% for polyuria; weight loss for no apparent reason was 14.9%; and polyphagia was 6.25%. The prevalence of classical symptoms was quite high in this study, but new diabetes was diagnosed after screening. This pattern was likely due to the subjects neglecting the symptoms that arise, ignoring the classical symptoms of diabetes, poverty, or stigma felt when suffering from diabetes. Symptoms of diabetes are often realized only after high blood glucose levels are known.

Specificity of the five risk factors, birth history of infants' weight ≥ 4 kg or GDM had the highest specificity of 90.9 % with a sensitivity of 22.5%. The sensitivity of the five risk factors also was found to be low.

A T2DM screening model should be developed, especially for populations with a family history of DM because of the high prevalence of T2DM. T2DM control programs are essential especially in high-risk populations so that a program can be done with early detection and prevention of T2DM complications. Promotion of a healthy lifestyle, a balanced diet, education about T2DM, and community participation is very important since diabetes complications often occur even after a patient is diagnosed with T2DM.

CONCLUSIONS

This study showed the prevalence of T2DM in populations with a family history of diabetes was quite high. Birth weight history ≥ 4 kg or GDM as factors associated with T2DM, while other clinical symptoms have a fairly high prevalence.

In women sensitivity of diabetes risk factors in populations with a family history of T2DM was quite high in those with a combination of risk factors including birth weight history of ≥ 4 kg or GDM with dyslipidemia, and a combination of birth weight ≥ 4 kg or GDM with dyslipidemia and hypertension, when a combination of the five common risk factors is studied.

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Ethical Approval and Informed Consent

This study was approved by The Medical and Health Research Ethical Committee (MHREC) from the Faculty of Medicine, Universitas Gadjah Mada,Yogyakarta with reference number KE/FK/698/EC/2015.

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Availability of Data and Material

Data and material can be accessed via corresponding author.

Conflicts of Interest

None.

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