1,000 Words←1,374 Words　Title〜Conclusion

Advice：

1.1020-1030 語くらいであれば Native Checker にまかせてもいいです。

2.Reviewer や Editor からのコメントで語数が増えるのはかまいません。削ったところに関連記載があるかもしれないので全バージョンは保存です。

Title

Undiagnosed diabetes has worse profiles for cardiovascular and metabolic markers than known diabetes

Summary

　We compared cardiovascular and metabolic markers between undiagnosed and known diabetes. We used a dataset of 34,282 subjects who voluntarily attended at health check-up. Subjects with undiagnosed diabetes had worse profiles of these markers than those with known diabetes. Undiagnosed diabetes should be recognized as a condition with these risks.

Introduction

　In type 2 diabetes, early detection and intervention is necessary to prevent complications such as cardiovascular disease. It has been reported, however, that the prevalence rate of 'undiagnosed' diabetes patients is an increasingly important public health issue[1]. Undiagnosed diabetes is defined as unknowingly having an elevated glucose level that meets the definition of diabetes[1].
　For example, there are an estimated 7.0 million persons with undiagnosed diabetes in the U.S. (2.2% of the whole population) [2]. Similarly, it has been reported that the prevalence of undiagnosed diabetes in the adult population of Manitoba was 2.2% in a Canadian

study[3]. If patients with diabetes are not diagnosed and are untreated, they may not have a chance to prevent future diabetes-related complications. Accordingly, risk factors or markers relevant to such complication may remain to be high in individuals of undiagnosed diabetes.

In our previous ~~study~~report[4], we conducted just a simple comparison between undiagnosed and diagnosed diabetes, which revealed that some risk indicators for lifestyle-related diseases were higher in subjects with undiagnosed diabetes than those with known diabetes. Therefore, in this study we compared cardiovascular and metabolic markers between subjects with undiagnosed and known diabetes, adjusting for major confounders such as age, sex and body mass index in a large Japanese population.

Methods

We used a dataset derived from the health screening program performed by the Yuport Medical Checkup Center in Tokyo from April 1998 to 2006. The details of this program has been reported elsewhere[5,6,7]. In total 97,585 persons (aged 25-64 years) participated in this health check-up. For repeat participants, the first-visit data was used for the study. The finally dataset comprised 34,282 persons for the analysis. According to the diagnostic criteria of diabetes by the Japan Diabetes Society[8] and American Diabetes Association[9]. We distributed these subjects into four separate groups; normal fasting plasma (NFG, <5.6 mmol/l) , impaired fasting glucose (IFG, 5.6-6.9 mmol/l), known diabetes and undiagnosed diabetes~~(Figure 1)~~. Known diabetes was identified when the participants reported irrespective of their fasting plasma glucose (FPG) levels. Undiagnosed diabetes was defined when FPG >= 7.0 mmol/l and the subjects did not report to have diabetes.

A blood sample was obtained after overnight fasting and measured at the Center's laboratory. For the measurements of fasting plasma glucose and hemoglobin A1c levels, a Toshiba TBA-40FR Autoanalyzer (Toshiba Medical Systems, Tokyo, Japan) was used. ~~Plasma glucose level was measured via the hexokinase-G6PD method (Denka Seiken, Niigata, Japan) with an inter-assay coefficient of covariation (CV) of 3.0% or less. HbA1c~~

コメント [Ci6]: 自分たちの先行研究は紹介するべき、同時になぜ本研究が新しいかも

コメント [Ci7]: 論文じゃないからこうする。あくまで学会発表で終わっているから。そのほうがこの論文を出したひとつの説明にもなる。

コメント [Ci8]: Brier report にしては語数が多い。517 語、主に Methods を削るべき。
1. 我々の先行研究を生かす
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~~level was measured by the latex immuno-agglutinin method (Determiner hemoglobin A1c, Kyowa Medex, Tokyo, Japan), with an inter-assay CV of 1.7-2.1%, which was comparable to that of plasma glucose and aligned to the Japan Diabetes Society (JDS) assigned values.~~ The JDS value of hemoglobin A1c were converted into NGSP units in this study by adding 0.4%{Seino, 2010 #2471}.

Other blood tests included serum levels of lipids and hepatic enzymes, and white blood cell count. Triglycerides, and total and HDL cholesterol were measured using enzymatic methods (reagents supplied by Daiichi Pure Chemicals, Tokyo, Japan). Aspartate aminotransferase and alanine aminotransferase were measured using enzymatic methods (reagents supplied by Denka Seiken, Niigata, Japan), as were gamma-glutamyltranspeptidase levels (Wako Junyaku, Osaka, Japan). White blood cell count was measured using the DC detection method (reagents supplied by Sysmex, Kobe, Japan).

All the evaluation procedures were performed in the same manner, ~~both~~ during the ~~baseline and follow-up~~ study periods~~, including blood measurements~~. ~~Height and weight were measured to calculate body mass index (BMI), which was defined as weight divided by height squared (kg/m2).~~ All analyses were performed using the SAS9.2 for Windows. Analysis of variance (ANOVA) tests adjusted for age and sex were used to compare the mean values at baseline among the four categorized groups according to FPG and HbA1c levels. <u>Because of their skewed distributions, serum levels of triglycerides, hepatic enzymes and white blood cell count were log-transformed for statistical analysis. For the four group comparisons, a p value of 0.005 was used to determine statistical significance since a Bonferroni correction was needed.</u> A cut-off p value of 0.05 was used for all the other statistical tests. ~~A cut-off p value <0.05 was used to determine statistical significance.~~ In accordance with the Private Information Protection Law, information that might identify subjects was kept private by the Center. Informed consent for anonymous participation in epidemiological research was obtained at every check-up.

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コメント [Ci10]: 下線の文章は Table 1 の脚注に入れるだけにして、本文の語数を節約。

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Results

From the 34,282 study subjects, we classified 23,491(68.5%), 8,786(25.6%) 795 (2.3%) and 1089 (3.2%) persons with NFG, IFG, known and undiagnosed diabetes, respectively. Among the 795 with known diabetes, 493 (54.0%) met the new criteria for diabetes.

Table 1 shows the comparisons of variables among the four groups, and between known and undiagnosed diabetes. In simple comparisons, age, BMI and the proportion of male were likely to increase across the four groups. In age, sex and BMI -adjusted comparisons of variables, systolic/diastolic blood pressures, serum levels of liver enzymes (alanine aminotransferase and gamma-glutamyl transpeptidase) and serum lipids (total cholesterol and triglycerides) were more likely to increase across the four subject groups. Conversely, HDL cholesterol was likely to decrease across the four subject groups.

There was no significant difference in sex distribution between the two groups. In age, sex and BMI -adjusted comparisons of variables, subjects with undiagnosed diabetes had higher FPG, HbA1c, body mass index, systolic/diastolic blood pressures, serum levels of liver enzymes (alanine aminotransferase and gamma-glutamyl transpeptidase) and serum lipids (total cholesterol and triglycerides) than those with known diabetes(Table1).

Accordingly, the prevalence of an abnormal range of these markers was higher in subjects with undiagnosed diabetes than those with known diabetes (Figure1).

Discussion

This study indicated that cardiovascular and metabolic markers such as blood pressure, serum lipids, and liver enzymes are higher in individuals with undiagnosed than those with known diabetes, even after adjusting for major confounders. Undiagnosed diabetes should be recognized as a condition with these risks.

Some studies have reported information concerning undiagnosed diabetes. For example, among those 70-years-old and over, undiagnosed diabetes patients who had heart disease show increased mortality rates in comparison with hospitalized diabetes patients who have

the same condition [10]. The prevalence of chronic kidney disease in undiagnosed diabetes patients was higher than these with clinical diabetes [11]. However, few studies have examined cardiovascular and metabolic markers in undiagnosed diabetes. Comparing with our previous report[4], we newly examined metabolic markers such as liver enzymes.

The results of our study may have clinical relevance in diabetes prevention. When considering interventions to change patients' lifestyle such as body weight and blood pressure reduction , it may be beneficial to focus on individuals with undiagnosed diabetes since they might remain at worse profiles than those with unknown diabetes.

コメント [Ci16]: Implication of this study

Some issues deserve to be mentioned as possible limitations. First, Since the study subjects participated on a voluntary basis, they may be healthier than the general population, causing a selection bias. Second, ~~we used a single fasting plasma glucose to diagnose diabetes, and did not utilize other diagnostic methods such as an oral glucose tolerance test. However, it is considered acceptable to base our analysis upon a single fasting glucose measurement for epidemiological estimates of diabetes prevalence and incidence [12, 13],.~~ ~~Third, T~~this study was a cross-sectional study. Therefore, the factor that causes undiagnosed diabetes is unknown. Diabetes at the time of diagnosis should have therapeutic intervention and should not be left as undiagnosed. Thus, a cross-sectional design is appropriate for this study.

コメント [Ci17]: Limitations, possible

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コメント [KI19]: ただし、他の箇所の削減で語数クリアなら、ここは復活です。

~~In summary, subjects with undiagnosed diabetes had worse profiles of cardiovascular and metabolic predictors than those with known diabetes. Undiagnosed diabetes should be recognized as a condition with these risks.~~

コメント [Ci20]: Summary はなくし、必要な箇所だけ Main Finding に持っていく

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with data collection.

Reference

［1］ Yiduo Zhang, Timothy M. Dall, Sarah E. Mann, Yaozhu Chen, Jaana Martin, Victoria Moore, Alan Baldwin, Viviana A. Reidel, and William W. Quick. Population Health Management. April 2009, 12(2): 95-101.

［2］ http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf

［3］ Young TK, Mustard CA. Undiagnosed diabetes: does it matter? CMAJ Canadian Medical Association Journal 2001;164:24-8.

［4］ Tomio J, Inoue K, Toyokawa S, Kobayashi Y. Examination of cases with fasting hyperglycemia detected in office health checkups: MY Health Up Study.[in Japanese] Conference Proceeding of Japanese Journal of Public Health. 2006;65:620.

［5］ Inoue K, Matsumoto M, Akimoto K. Fasting plasma glucose and HbA1c as risk factors for Type 2 diabetes. Diabet Med. 2008;25(10):1157-63.

［6］ Inoue K, Matsumoto M, Akimoto K. The threshold for definition of impaired fasting glucose in a Japanese population. Diabet Med. 2009;26(11):1175-8.

［7］ 印刷中 Diabet Med. 2011 Dec 12. doi: 10.1111/j.1464-5491.2011.03536.x. [Epub ahead of print]

［8］ Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997;20(7):1183-97.

［9］ Report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus. Journal Japan Diab Soc. 1999;42(5):385-404.

［10］、Flores-Le Roux JA, Comin J , Pedro-Botet J , Benaiges D , Puig-de Dou J　Chillarón JJ , Goday A　Bruguera J, Cano-Perez JF.Seven-year mortality in heart failure patients with undiagnosed diabetes: an observational　study.　CardiovascDiabetol2011;10:39

［11］ Flores-Le Roux JA , Comin J , Pedro-Botet J , Benaiges D , Puig-de Dou J , Chillarón JJ , Goday A , Bruguera J , Cano-Perez JF　Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes.ClinJAmSoc Nephrol2010;5:673-82

［12］ Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20: 1183-1197.

［13］ Report of the Japan Diabetes Society Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus [in Japanese]. J Japan Diab Soc 1999; 42: 385-404.

Table1. Subject Characteristics

Characteristics	NFG	IFG	Known Diabetes	Undiagnosed Diabetes	P value Adjusted by Sex & Age BMI	
	n＝23491	n＝8786	n＝916	n＝1089	4 groups	2 groups Known vs. Undiagnosed diabetse
Fasting plasma glucose (mmol/l)	5.0 ± 0.32	5.9 ± 0.3	8.0 ± 2.4	8.9 ± 2.3	<.0001	<.0001
HbA1c (%)	4.8 ± 0.4	5.2 ± 0.5	6.9 ± 1.6	7.1 ± 1.8	<.0001	<.0035
Age (years)	49.8 ± 13.3	55.3 ± 11.6	60.3 ± 8.0	58.6 ± 10.4	<.0001	<.0002
Male sex, n (%)	9879 (42.1)	5779 (65.8)	650 (71.3)	781 (71.7)	<.0001	0.8081
BMI (kg/m^2)	22.3 ± 2.9	24.0 ± 3.1	23.9 ± 3.1	24.9 ± 3.5	<.0001	<.0001
Systolic blood pressure (mmHg)	120 ± 17	131 ± 18	131 ± 17	137 ± 19	<.0001	<.0001
Diastolic blood pressure (mmHg)	73 ± 11	80 ± 11	78 ± 10	83 ± 11	<.0001	<.0001
Triglycerides (mmol/l)	0.93 (0.67 - 1.35)	1.24 (0.89 - 1.79)	1.33 (0.92 - 1.85)	1.54 (1.07 - 2.30)	<.0001	<.0001
Total cholesterol (mmol/l)	199.6 ± 35.1	208.1 ± 35.4	202.0 ± 34.4	214.0 ± 38.1	<.0001	<.0001
HDL cholesterol (mmol/l)	59.1 ± 14.8	54.5 ± 14.0	52.3 ± 13.8	51.1 ± 12.7	<.0001	<.00219
Asparate aminotransferase (U/l)	20(17 to 24)	22(19 to 27)	22(18 to 27)	24(19 to 31)	<.0001	<.0001
Alanine aminotransferase (U/l)	17 (13 to 23)	21(16 to 32)	22(16 to 32)	26(19 to 39)	<.0001	<.0001
γ -Glutamyltranspeptidase (U/l)	17(11 to 28)	26(16 to 47)	25(15 to 46)	38(23 to 72)	<.0001	<.0001
Uric acid (mg/dl)	5.1 ± 1.3	5.8 ± 1.4	5.4 ± 1.3	5.6 ± 1.4	<.0001	<.0001

Data are expressed as mean ± SD, median (25th percentile, 75th percentile) or number (%). Probability values are for comparison of cartegories of means (analysis of variance for age and body mass index and analysis of variance adjusted by sex, age and body mass index for the other variables) or percentages (chi-square test). For comparison of means of triglycerides, aspartate aminotransferase, alanine aminotransferase and γ-glutamyltranspeptidase were log-transformed for their skewed distributions.

Figure 2. Frequencies of subjects with worse profiles of cardiovascular and metabolic markers per four categories
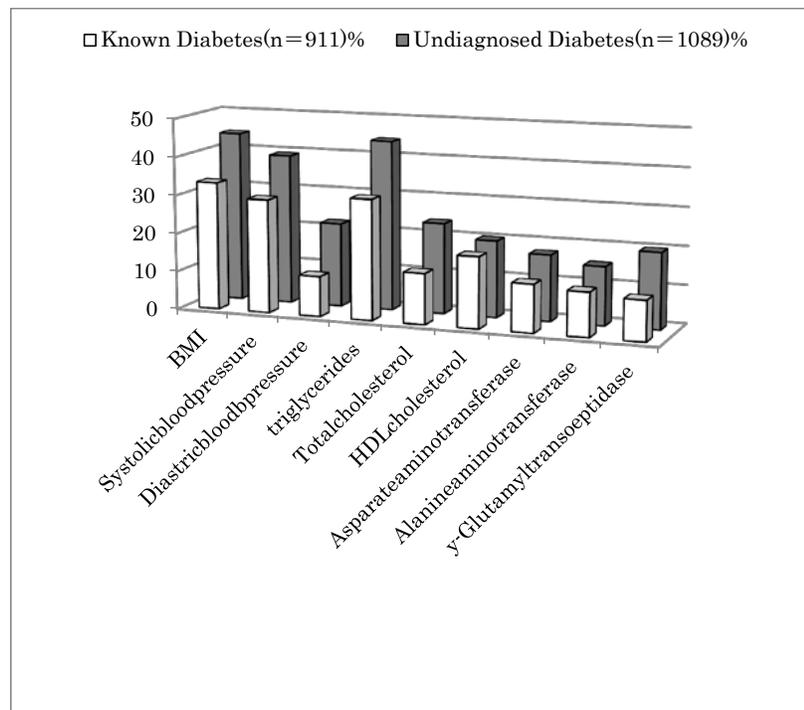
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  As such, these results may have clinical relevance in diabetes prevention. We examined cardiovascular and metabolic risk factors in individuals with undiagnosed (unknown and newly diagnosed) diabetes using current diagnostic criteria to compare to individuals with known diabetes.

When considering interventions such as changing patients' lifestyle, thus, it may be beneficial to focus on undiagnosed diabetes.

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After controlling for age, sex and BMI

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Methods

We used a dataset derived from the health screening program performed by the Yuport Medical Checkup Center in Tokyo from April 1998 to 2006. The details of this program has been reported elsewhere[5,6,7]. In total 97,585 persons (aged 25-64 years) participated in this health check-up. For repeat participants, the first-visit data was used for the study. The finally dataset comprised 34,282 persons for the analysis. According to the diagnostic criteria of diabetes by the Japan Diabetes Society[8] and American Diabetes Association[9]. We distributed these subjects into four separate groups; normal fasting plasma (NFG, <5.6 mmol/l) , impaired fasting glucose (IFG, 5.6-6.9 mmol/l), known diabetes and undiagnosed diabetes(Figure 1). Known diabetes was identified when the participants reported irrespective of their fasting plasma glucose (FPG) levels. Undiagnosed diabetes was defined when FPG >= 7.0 mmol/l and the subjects did not report to have diabetes.

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All the evaluation procedures were performed in the same manner, during the study periods. All analyses were performed using the SAS9.2 for Windows. Analysis of variance

(ANOVA) tests adjusted for age and sex were used to compare the mean values at baseline among the four categorized groups according to FPG and HbA1c levels. A cut-off p value of 0.05 was used for all the other statistical tests.

In accordance with the Private Information Protection Law, information that might identify subjects was kept private by the Center. Informed consent for anonymous participation in epidemiological research was obtained at every check-up.