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ORIGINAL ARTICLE

Sex differences in predictive factors for onset of type 2 diabetes in Japanese individuals: A 15-year follow-up study

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ABSTRACT

Aims/Introduction: The increase in the number of patients with type 2 diabetes mellitus is an important concern worldwide. The goal of this study was to investigate factors involved in the onset of type 2 diabetes mellitus, and sex differences in long-term follow up of people with normal glucose tolerance.

Materials and Methods: Of 1,309 individuals who underwent screening at our facility in 2004, 748 individuals without diabetes were enrolled. Correlations of metabolic markers including serum adiponectin (APN) with onset of type 2 diabetes mellitus were examined over 15 years in these individuals.

Results: The Kaplan–Meier curve for onset of type 2 diabetes mellitus for 15 years in the decreased APN group was examined. Hazard ratios for the APN concentration for onset of diabetes were 1.78 (95% confidence interval [CI] 1.20–2.63, $P = 0.004$) in all participants, 1.48 (95% CI 0.96–2.29, $P = 0.078$) for men and 3.01 (95% CI 1.37–6.59, $P = 0.006$) for women. During the follow-up period of 15 years, body mass index, estimated glomerular filtration rate, fatty liver, C-reactive protein and alanine aminotransferase in men were significant in univariate analysis, but only estimated glomerular filtration rate and fatty liver were significantly related to onset of type 2 diabetes mellitus in multivariate analysis. In women, body mass index, systolic blood pressure, triglyceride, fatty liver and APN were significant in univariate analysis, and APN was the only significant risk factor in multivariate analysis ($P < 0.05$).

Conclusions: There are differences between men and women with regard to targets for intervention to prevent the onset of type 2 diabetes mellitus. Individuals requiring intensive intervention should be selected with this finding to maximize the use of limited social and economic resources.

INTRODUCTION

The increase in cases of type 2 diabetes mellitus is an important concern worldwide, and has been suggested to be due to genetic, environmental and lifestyle factors. Diabetes is a systemic disease, and medical costs for complications, such as nephropathy, dialysis and the high associated rate of cardiovascular events, are causing problems in many countries[1–4]. Onset of type 2 diabetes mellitus is linked to insulin resistance and decreased insulin secretion. Insulin resistance is difficult to evaluate clinically, but some risk factors have been identified. These include adiponectin (APN), which has been widely reported to reflect insulin sensitivity[5,6].

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Adiponectin (Acrp30, adipoQ) was discovered through complementary deoxyribonucleic acid cloning[7–10], and there is increasing evidence that hypoadiponectinemia is involved in the pathogenesis of atherosclerosis and insulin resistance[11,12]. In transgenic or knockout mice and other studies, APN mediates features of metabolic syndrome, including obesity, insulin resistance, type 2 diabetes mellitus, coronary heart disease and lipodystrophy[12,13]. In addition to improving insulin resistance, APN might have anti-inflammatory, anti-arteriosclerosis and anti-cognitive effects[6]. Receptors for APN have been identified and APN-related therapeutic agents are being developed[14]. Signal transduction has been linked to APN activation of 5′ adenosine monophosphate-activated protein kinase, and to binding of T-cadherin to APN receptors R1 and R2[14–16]. APN is also important in gestational diabetes[17], and low APN has recently been associated with aggravation of coronavirus disease-2019 infection[18].

There have been some reports on serum adiponectin levels and the onset of diabetes. Here, we re-examined the results of 15-year follow up of individuals with normal blood glucose who attended our Preventive Medicine Research Center, and onset of type 2 diabetes mellitus was evaluated based on various clinical indicators, including serum APN, and by sex, with the goal of identifying risk factors for identification of individuals in whom early-stage interventions should be implemented to prevent diabetes onset.

MATERIALS AND METHODS

A total of 1,309 people visited the Preventive Medicine Research Center at Asahi General Hospital, Asahi, Japan, from April 2004 to March 2005. A total of 748 of these individuals were included in the present study (Figure 1). People who did not visit for 1,000 days after the first visit were excluded. Fatty liver was diagnosed by abdominal ultrasound echography. Four criteria used for this diagnosis (hepatorenal echo contrast, liver brightness, deep attenuation and vascular blurring) were evaluated by hepatologists[19]. Type 2 diabetes mellitus was diagnosed based on fasting plasma glucose (FPG) ≥126 mg/dL, glycated hemoglobin (HbA1c) ≥6.5% (46.57 mol/mol), postprandial plasma glucose ≥200 mg/dL, self-reported diagnosis by a physician and/or taking insulin or an oral antidiabetic agent.

The onsets of diabetes were confirmed at the visits for health checkup, because all participants did not visit every year. Hypertension was diagnosed based on systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; obesity was defined as body mass index (BMI) ≥25 kg/m^2 according to Japanese standard categories; and dyslipidemia was diagnosed based on low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL or fasting triglyceride ≥150 mg/dL. Current and past smokers were defined as smokers, and those who had never smoked were defined as non-smokers. Serum APN was measured by enzyme-linked immunosorbent assay to detect monomeric APN (Otsuka, Tokyo, Japan).

Statistical analysis

Baseline characteristics are presented as means (±standard deviation) for continuous variables, as a number (%) for categorical variables and stratified by sex. A receiver operating characteristic curve was drawn for APN levels with onset of diabetes as an event, and the APN level giving the best sensitivity and specificity was determined. Participants were divided into those in which APN was high (>6.53 μg/mL) and low (≤6.53 μg/mL) in all participants, high (>5.36 μg/mL) and low (≤5.36 μg/mL) in men, and high (>8.52 μg/mL) and low (≤8.52 μg/mL) in women. Univariate analysis was carried out using the Kaplan–Meier method and a competing risks model. Changes in serum APN over time were examined by the paired *t*-test and stratified by sex. To identify predictors of onset and risk factors for developing diabetes, factors found to be significant in univariate analysis were included in multivariate analysis using a Fine–Gray model. Statistical significance was defined as $P < 0.05$ in all analyses. All analyses were carried out using R ver. 4.0.3 with the package survival (https://www.r-project.org/ accessed 11 October 2020).

RESULTS

Of the 1,309 participants who underwent screening at our facility in 2004, 1,199 were approved for measurement of APN, of whom 283 were diagnosed with diabetes or diabetic plasma glucose and hemoglobin abnormalities, and 916 did not have diabetes (Figure 1). Among the participants without diabetes, 162 with a short follow-up period were excluded, along with five cases with participants and one participant diagnosed with nephrotic syndrome after 2004. Finally, 748 participants were included in the study.

In 15 years, 108 participants (83 men, 25 women) developed diabetes, and 630 participants (447 men, 193 women) did not develop diabetes. Comparison of baseline parameters between the onset and non-onset groups (Table 1) showed significant differences in age, obesity, FPG, postprandial plasma glucose, HbA1c, eGFR, uric acid, alanine aminotransferase (ALT), fatty liver and serum APN. There were significant differences in age, obesity, FPG, postprandial plasma glucose, HbA1c, eGFR, CRP, ALT and fatty liver in men; and in hypertension, FPG, HbA1c, uric acid and fatty liver in women.

The areas under the curve in receiver operating characteristic analysis for APN and onset of diabetes for 15 years were 0.59 in all participants, 0.55 (95% confidence interval [CI] 0.49–0.62) in men and 0.63 (95% CI 0.50–0.76) in women (Figure 2a–c). Using the cut-off for the APN concentration (Figure 2), Kaplan–Meier analysis for onset of diabetes for 15 years showed hazard ratios for the APN concentration of 1.78 (95% CI 1.20–2.63, $P = 0.004$) for all participants, 1.48 (95% CI 0.96–2.29, $P = 0.078$) for men and 3.01 (95% CI 1.37–6.59, $P = 0.006$) for women, with significant differences for all participants and for women (Figure 3a–c).

Changes in serum APN over time were examined by the paired *t*-test for 190 men and 80 women who were examined

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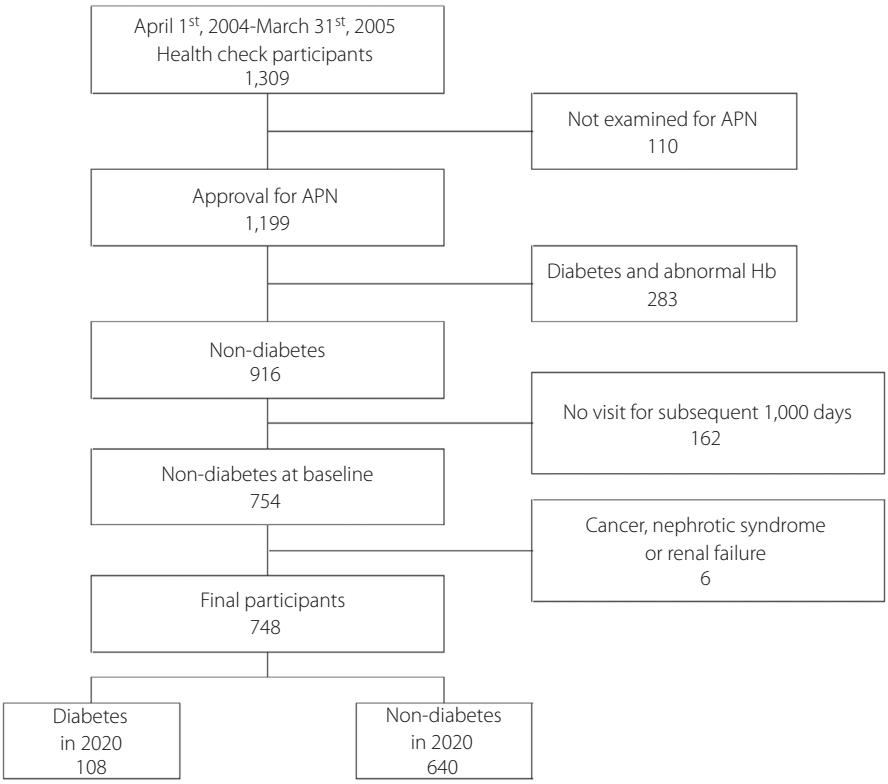

Figure 1 | Flow diagram of selection of participants at baseline. APN, adiponectin; Hb, hemoglobin.

at 3 and 5 years after baseline. APN levels at baseline and after 3 and 5 years were 6.3 ± 2.8, 6.4 ± 3.0 and 6.5 ± 3.1 μg/mL, respectively, in men (Figure 4a), and 11.2 ± 5.2, 11.8 ± 5.6 and 10.9 ± 5.5 μg/mL in women (Figure 4b). There were no significant changes from the baseline levels of APN.

Univariate and multivariate analyses were used to examine factors that influenced the onset of type 2 diabetes for 15 years. In all participants, BMI, triglyceride, eGFR, fatty liver, CRP, ALT and APN (≤6.53 μg/mL) were significant factors in univariate analysis, but only BMI, eGFR and fatty liver remained significant in multivariate analysis, and APN was no longer significant (Table 2). In men, BMI, eGFR, fatty liver, CRP and ALT were significant in univariate analysis, but only eGFR and fatty liver were significant in multivariate analysis; whereas in women, BMI, systolic blood pressure, triglyceride, fatty liver and APN were significant in univariate analysis, and APN was the only significant risk factor in multivariate analysis. Some participants died during the 15-year observation period, but the causes of death were not due to cardiovascular events (data not shown).

DISCUSSION

In the present study, we analyzed the relationship between APN, which is related to insulin resistance that occurs in the early stage of diabetes, and onset of diabetes in long-term follow up. Onset of diabetes involves many lifestyle-related and genetic factors, and low serum APN was found to be an important predictor, especially in women. However, there was no significant change in APN levels found for 5 years, suggesting that it might be difficult to elevate serum APN only by lifestyle-related improvement. The area under the curve, specificity and sensitivity of the APN level for diabetes onset were not high, even in women. This might be because onset of diabetes involves many factors, including insulin resistance, insulin secretion and genetic factors using genome-wide polygenic scores, and it might not be possible to find an association with a single factor, such as the APN level[20,21].

Kaplan–Meier analysis showed a significant increase in onset of type 2 diabetes mellitus over 15 years in all participants and in women with low APN. The significant effect of low APN in all participants was influenced by the data in women, which shows that it is important to evaluate onset of diabetes separately for men and women. In multivariate analysis, the APN level was a significant factor for onset of type 2 diabetes mellitus in women. There was a difference in the baseline level of APN in men and women, and the threshold of APN level at the onset of diabetes might differ between men and women[22,23]. Female hormones affects APN levels[22], and although APN decreases after menopause in women, it might still be a factor associated with the onset of diabetes. A cross-sectional study of

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Table 1 | Baseline characteristics of participants based on 15-year new-onset type 2 diabetes status

Parameter	Total	Incident type 2 diabetes		*P*-value	Men	Incident type 2 diabetes		*P*-value	Women	Incident type 2 diabetes		*P*-value
		No	Yes			No	Yes			No	Yes	
n	748	640	108		530	447	83		218	193	25	
Sex (male)	530 (71%)	447 (70%)	83 (77%)	0.169								
Age (years)	54.0 ± 8.7	53.7 ± 8.8	56.0 ± 8.1	0.009	53.4 ± 9.0	53.0 ± 9.1	56.0 ± 8.2	0.005	55.5 ± 7.8	55.4 ± 7.8	56.2 ± 7.6	0.606
Obesity, *n* (%)	251 (34%)	196 (31%)	55 (51%)	<0.001	207 (39%)	162 (36%)	45 (54%)	0.003	44 (20%)	34 (18%)	10 (40%)	0.015
Hypertension, *n* (%)	89 (12%)	70 (11%)	19 (18%)	0.054	73 (14%)	59 (13%)	14 (17%)	0.387	16 (7%)	11 (6%)	5 (20%)	0.024
Dyslipidemia, *n* (%)	361 (48%)	301 (47%)	60 (56%)	0.118	286 (54%)	237 (53%)	49 (59%)	0.339	75 (34%)	64 (33%)	11 (44%)	0.371
Smoking habit, *n* (%)	236 (32%)	198 (31%)	38 (35%)	0.373	230 (43%)	192 (43%)	38 (46%)	0.632	6 (3%)	6 (3%)	0 (0%)	1.000
FPG (mg/dL)	95.9 ± 8.4	94.8 ± 7.7	102.4 ± 9.6	<0.001	97.1 ± 8.2	96.0 ± 7.5	103.0 ± 8.9	<0.001	92.9 ± 8.4	92.0 ± 7.3	100.4 ± 11.9	<0.001
PPG (mg/dL)	141.1 ± 29.6	138.3 ± 29.2	158.1 ± 26.0	<0.001	141.1 ± 29.7	137.7 ± 29.2	159.3 ± 25.6	<0.001	141.3 ± 29.5	139.6 ± 29.4	154.1 ± 27.5	0.020
HbA1c (%)	5.69 ± 0.34	5.63 ± 0.32	6.02 ± 0.29	<0.001	5.69 ± 0.34	5.64 ± 0.32	5.99 ± 0.29	<0.001	5.68 ± 0.34	5.62 ± 0.31	6.12 ± 0.27	<0.001
eGFR (mL/min/1.73 m^2)	76.7 ± 12.2	77.2 ± 12.3	73.5 ± 11.1	0.004	76.6 ± 11.8	77.4 ± 11.8	72.4 ± 10.7	<0.001	76.8 ± 13.1	76.7 ± 13.3	77.2 ± 11.9	0.852
Uric acid (mg/dL)	5.54 ± 1.36	5.49 ± 1.36	5.86 ± 1.33	0.008	6.01 ± 1.22	5.98 ± 1.20	6.17 ± 1.27	0.209	4.40 ± 0.95	4.34 ± 0.93	4.85 ± 1.00	0.013
CRP (mg/dL)	0.07 ± 0.24	0.07 ± 0.24	0.11 ± 0.24	0.139	0.07 ± 0.20	0.07 ± 0.19	0.12 ± 0.26	0.034	0.07 ± 0.30	0.08 ± 0.32	0.06 ± 0.12	0.863
AST (IU/L)	24.0 ± 10.6	23.8 ± 10.8	25.2 ± 9.0	0.211	24.9 ± 10.6	24.7 ± 10.8	25.9 ± 9.4	0.356	22.0 ± 10.2	21.8 ± 10.5	23.0 ± 7.0	0.582
ALT (IU/L)	25.1 ± 15.4	24.3 ± 14.8	29.6 ± 18.2	0.001	27.7 ± 16.1	26.9 ± 15.4	31.9 ± 19.0	0.009	18.7 ± 11.2	18.2 ± 11.0	21.9 ± 12.4	0.124
Fatty liver	248 (33%)	193 (30%)	55 (51%)	<0.001	196 (37%)	153 (34%)	43 (52%)	0.003	52 (24%)	40 (21%)	12 (48%)	0.005
APN (μg/mL)	7.72 ± 4.38	7.90 ± 4.43	6.66 ± 3.98	0.006	6.13 ± 2.84	6.21 ± 2.88	5.68 ± 2.63	0.116	11.60 ± 5.01	11.82 ± 4.89	9.93 ± 5.72	0.076

Values are means ± standard deviation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; PPG, postprandial plasma glucose.

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	AUC	AUC 95%CI	Cut off (μg/mL)	Specificity	Sensitivity	100% Sensitivity (μg/mL)
Total	0.59	0.53-0.65	6.53	50.9%	63.9%	21.83
Men	0.55	0.49-0.62	5.36	52.1%	57.8%	15.30
Women	0.63	0.50-0.76	8.52	72.5%	56.0%	21.83

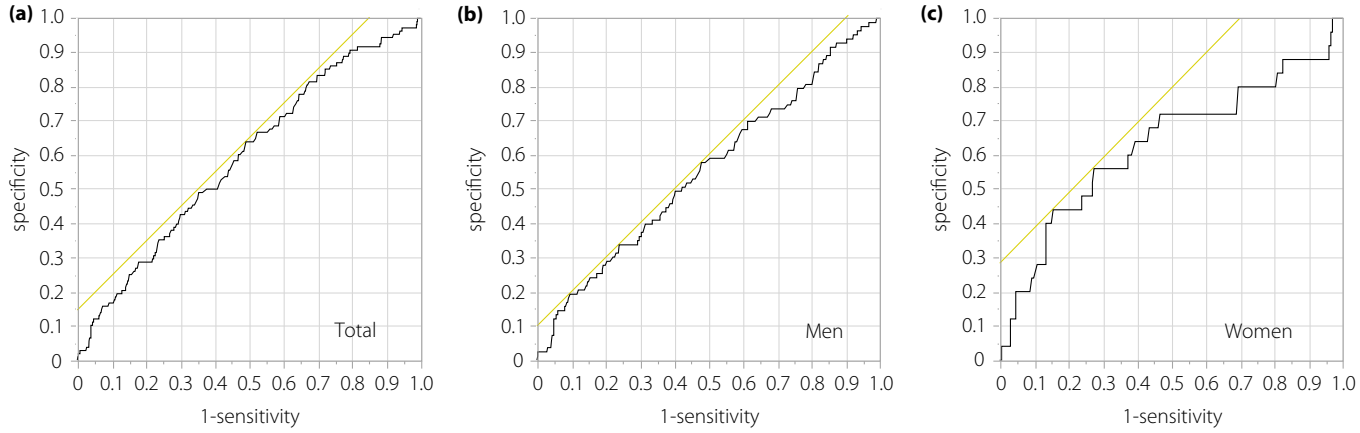

Figure 2 | Receiver operating characteristic curves for APN levels with onset of diabetes. Areas under the curve (AUCs) of the receiver operating characteristic curves for APN are shown for (a) all participants, (b) men and (c) women.

the onset of diabetes in men and women suggested differences in metabolic indicators as a result of differences in fat distribution[24]. The prevalence of the onset of diabetes also differs by sex, and women are older at the time of onset[25,26]. Factors that affect the onset of diabetes include the androgen/estrogen ratio, body composition and energy consumption[22,27].

Several studies have examined the relationship of serum APN levels with insulin sensitivity and arteriosclerosis, and a cross-sectional meta-analysis study showed the relationship between the level of circulating APN and prediabetes[28], but not so many reports have considered APN and onset of type 2 diabetes mellitus by follow-up studies. Follow-up periods have varied in meta-analyses[23,26], and have been shorter than that in the current study. The Framingham study also had a relatively short observation period, but the onset of diabetes was found to be low in participants with high APN levels[29]. The well-known Diabetes Prevention Program also reported a short-term relationship between the onset of diabetes and adiponectin levels. In this paper, even with bodyweight adjusted, adiponectin levels were an important factor in the development of diabetes across races and sexes[30]. Although the follow-up periods were not long in Japan, there are some reports on adiponectin levels and the onset of diabetes[31]. However, the difference between men and women has not been considered. Based on these previous studies, one strength of the present study is the long follow-up period.

Regarding the incidence of diabetes, it has been reported that APN had a stronger effect in women than in men[32–34], although not directly compared in detail, which is consistent with the present results. These findings suggest that APN is a common factor in the development of diabetes in women, regardless of race or lifestyle, and decreased APN levels have been found to be significant in pregnant women. Low APN has also been found to predict the onset of gestational diabetes and to induce hepatic fat accumulation in gestational diabetic mice, and APN supplementation can prevent fat accumulation and suppress intramuscular fat accumulation[17,35–37].

A recent report showed that APN in adipose tissue around blood vessels controls vascular function[38,39]. In IRS-2 knockout mice, Kadowaki *et al.*[40] found that an impaired insulin signal in the vascular endothelium might reduce insulin transfer to skeletal muscle and reduce glucose uptake, leading to the onset of diabetes through decreased nitric oxide (NO) synthesis. Nitric oxide is activated by estrogen, and the difference in low and high levels of APN in women at onset of diabetes might cause a difference in the response of the vascular endothelium due to the action of estrogen[41,42]. However, it is clear that female hormones alone cannot explain the difference in the onset of diabetes between men and women, as the present participants had an average age of ≥50 years. Changes in inflammatory cytokines might occur due to a difference in distribution of fat accumulation up to this age, and these long-term effects might be responsible for the onset of diabetes. Recently, it was reported that severe acute respiratory syndrome coronavirus 2 infection induces a higher prevalence of diabetes

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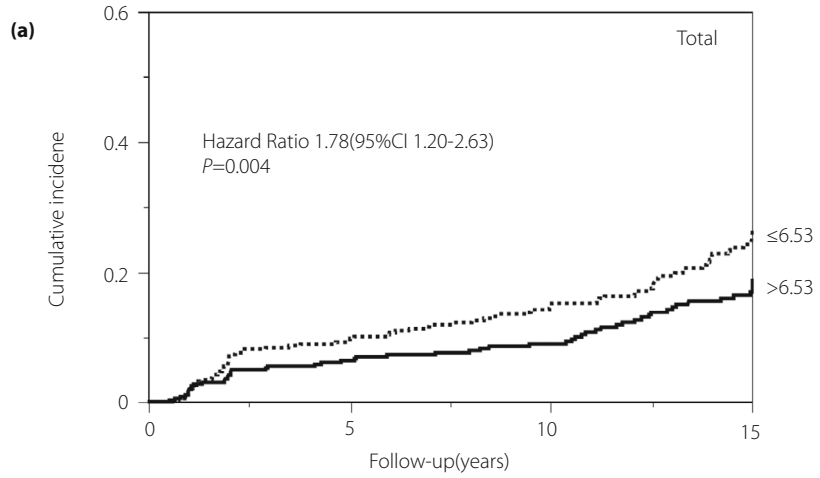
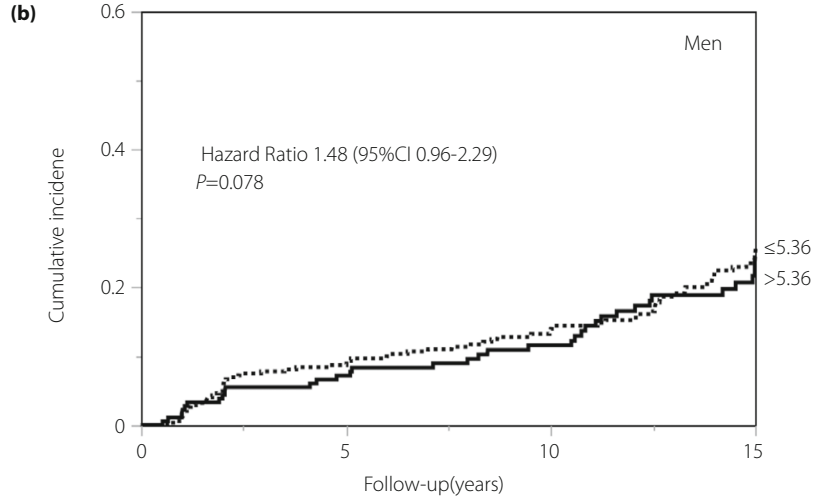
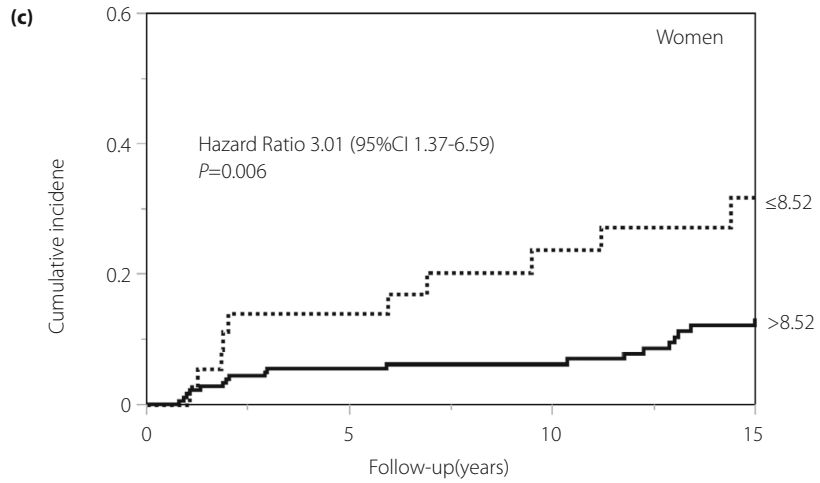


APN≤6.53 μg/ml	383	315	239	141
APN>6.53 μg/ml	365	317	257	163



APN≤5.36	347	286	217	129
APN>5.36	183	161	129	80



APN≤8.52 μg/ml	36	29	22	12
APN>8.52 μg/ml	182	156	125	83

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Figure 3 | Kaplan–Meier analysis of onset of type 2 diabetes in (a) all participants, (b) men and (c) women. There was a significant increase in onset of type 2 diabetes in women with low adiponectin (APN), but not in men with low APN.

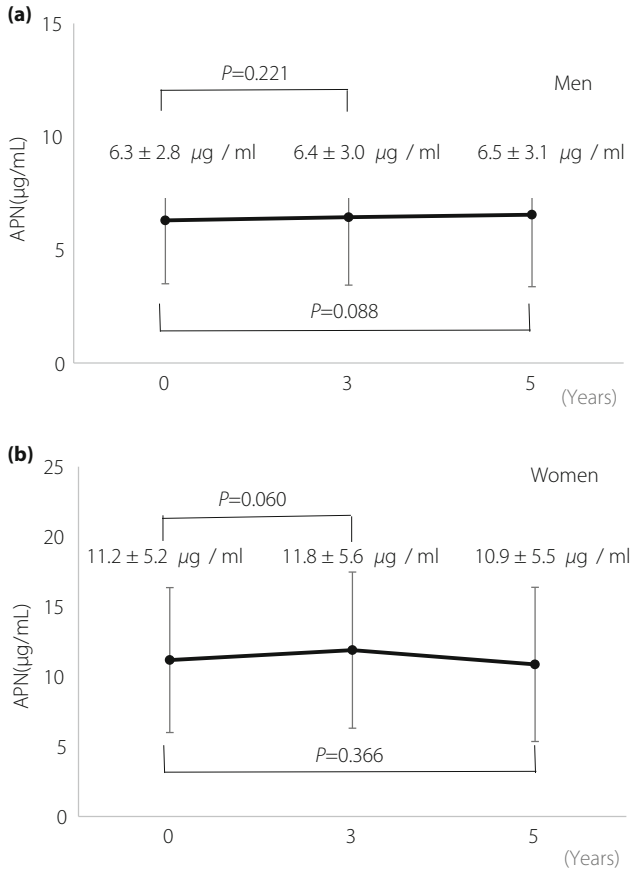

Figure 4 | Changes in APN levels from baseline for 5 years in (a) men (n = 190) and (b) women (n = 80). There was no significant change in either sex (paired t-test). Values are shown as the mean ± standard deviation.

in men than in women with higher APN, suggesting that causes of hyperglycemia differ by sex[18,43].

In men, decreased eGFR was identified as a predictor for the onset of type 2 diabetes mellitus. In our previous report in men with normal glucose tolerance, decreased eGFR and hyperferritinemia were found to be significant predictive markers for the onset of type 2 diabetes[44]. A similar relationship between decreased eGFR and onset of diabetes was also found in another study[45]. There is a known sex difference in the onset of cardiovascular disease, and some reports have shown differences between men and women in the development of diabetic nephropathy[46]. The mechanism of eGFR reduction and diabetes onset in men is unclear, but eGFR reduction is a manifestation of systemic arteriosclerotic lesions in men, and might cause systemic inflammation and increased oxidative stress. Hypertension, dyslipidemia, obesity, insulin resistance, smoking and genetic factors leading to atherosclerosis are believed to be the underlying risk factors for the decrease in eGFR in men. These factors might also be responsible for the development of diabetes[47,48], because atherosclerotic changes are well-known to be more prevalent in men than in women. Decreased osteocalcin has also been associated with reduced renal function and increased onset of diabetes[49–51], which might be one of the topics for future studies.

Fatty liver was found to be a significant risk factor for diabetes in men, but not in women. The sex difference in the incidence of fatty liver and diabetes might largely be due to the difference in fat accumulation between men and women[22,27,52]. Visceral fat obesity is more common in men, whereas subcutaneous fat obesity is more frequent in women. Therefore, even with the same fatty liver, the effect on diabetes onset might be lower in women. In addition, the onset of fatty liver in women has been found to occur 10 years after menopause[53,54], and changes in fat accumulation and increased fatty liver might delay onset of diabetes in women. The favorable role of estrogen in chronic disease with hepatitis B infection suggests that estrogen has a potent endogenous anti-oxidant effect that might suppress fatty liver damage and insulin resistance[55]. Alcohol is also a factor in fatty liver in men, and the characteristics of fatty liver might differ between the sexes. These findings suggest that the onset of type 2 diabetes mellitus, diabetic complications and chronic diseases related to arteriosclerosis need to be considered from a perspective of sex differences.

We previously reported a case of Werner's syndrome with APN gene abnormality, and we found that pioglitazone caused an increase in serum APN even in this case, in which there was secretory abnormality[56]. One study on the prevention of diabetes with troglitazone by the Diabetes Prevention Program group has also been reported, but the effect of drugs was temporary and disappeared when it was stopped[57]. Many studies showed that APN has an anti-inflammatory effect, but some also suggest that APN causes inflammation in certain cells. Acute effects, chronic effects and differences depending on the tissue are likely, but require further clarification. The Diabetes Prevention Program is a clinical study with the aim of reducing progression using metformin and lifestyle interventions in early-stage diabetes, but that study showed the difficulties of intervention and changes in adiponectin were comparatively small and less strongly related to diabetes outcome than baseline APN levels[30,58]. Given that there are no clear biomarkers that can be used to trigger an intervention, one method might be to consider the intervention separately for men and women[59].

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Table 2 | Hazard ratios for incidence of type 2 diabetes in univariate and multivariate analyses

Parameter	Total				Men				Women			
	Univariate HR (95% CI)	*P*-value	Multivariate aHR (95% CI)	*P*-value	Univariate HR (95% CI)	*P*-value	Multivariate aHR (95% CI)	*P*-value	Univariate HR (95% CI)	*P*-value	Multivariate aHR (95% CI)	*P*-value
Sex (male)	1.39 (0.89–2.18)	0.150										
BMI ≥25 kg/m^2	2.31 (1.58–3.37)	<0.001	1.62 (1.03–2.55)	0.039	2.04 (1.33–3.15)	0.001			3.09 (1.39–6.87)	0.006	1.10 (0.99–1.21)	0.085
SBP ≥140 mmHg	1.56 (0.91–2.67)	0.100			1.16 (0.60–2.21)	0.660			3.87 (1.51–9.95)	0.005	2.60 (0.97–6.91)	0.056
DBP ≥90 mmHg	1.52 (0.75–3.07)	0.240			1.42 (0.66–3.02)	0.370			1.72 (0.26–11.57)	0.570		
TG ≥150 mg/dL	1.65 (1.10–2.46)	0.015			1.35 (0.86–2.11)	0.190			4.00 (1.49–10.8)	0.006	2.49 (0.99–6.27)	0.054
HDL <40 mg/dL	0.81 (0.41–1.61)	0.550			0.79 (0.40–1.60)	0.520						
LDL ≥140 mg/dL	1.24 (0.83–1.86)	0.280			1.26 (0.80–1.99)	0.320			1.18 (0.51–2.72)	0.700		
eGFR <70 mL/min/1.73 m^2	2.01 (1.37–2.93)	<0.001	1.93 (1.32–2.81)	0.001	2.51 (1.63–3.85)	<0.001	2.36 (1.53–3.65)	<0.001	1.07 (0.47–2.42)	0.880		
Fatty liver	2.26 (1.56–3.30)	<0.001	1.68 (1.07–2.62)	0.024	1.96 (1.27–3.00)	0.002	1.63 (1.04–2.56)	0.033	3.28 (1.49–7.20)	0.003		
Uric acid ≥7.0 mg/dL	1.49 (0.94–2.35)	0.090			1.41 (0.87–2.27)	0.160						
CRP ≥0.1 mg/dL	1.69 (1.15–2.47)	0.007			1.82 (1.18–2.80)	0.007	1.50 (0.95–2.34)	0.079	1.15 (0.49–2.74)	0.750		
ALT ≥50 IU/L	2.21 (1.30–3.77)	0.004			1.99 (1.13–3.49)	0.017	1.58 (0.89–2.80)	0.120	4.49 (0.75–26.9)	0.100		
APN ≤6.53 μg/mL	1.78 (1.20–2.63)	0.004	1.38 (0.91–2.08)	0.130	1.48 (0.96–2.29)	0.078			3.01 (1.37–6.59)	0.006	2.35 (1.09–5.03)	0.029

aHR, adjusted hazard ratio; ALT, alanine aminotransferase; APN, adiponectin; CRP, C-reactive protein; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglyceride.

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There were some limitations to the present study. First, measurement of APN was for the globular type. A difference in receptor binding between monomer and multimer APN has been shown, but the APN R1 receptor is thought to be the main factor related to glucose metabolism[14]. Also, a meta-analysis showed that the same clinical results are obtained regardless of the APN measurement method[23]. Second, it is unknown if improvements in lifestyle, such as eating habits or exercise, occurred during the course of 15 years. Third, it is uncertain if there were changes in APN levels during the 15-year period, but there was no significant change of APN from baseline in a subgroup of participants after 5 years. There might have been some variation in the low and high APN groups, but this was probably not major. Fourth, the study was limited to a single facility. However, the results for APN levels and onset of diabetes in women are consistent with findings worldwide, and are unlikely to be facility-specific or due to specific circumstances.

In conclusion, low serum APN in women and decreased eGFR in men were found to increase the onset of diabetes significantly in 15-year follow up. The incidence of type 2 diabetes is expected to increase worldwide, and lifestyle interventions for all people might be difficult due to limited social and economic resources. Therefore, the results of the present study provide good markers for the selection of individuals who require intervention in lifestyle-related habits, such as diet and exercise, for prevention of the onset of diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The ethics committee of Asahi General Hospital approved the study on 20 January 2021 (Approval No. 2021011913). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent: We applied the opt-out methods to obtain informed consent for this study.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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