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REVIEW ARTICLE

Associations of impaired glucose metabolism and dyslipidemia with cardiovascular diseases: what have we learned from Japanese cohort studies for individualized prevention and treatment?

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Abstract Metabolic disorder is a modifiable risk factor for cardiovascular diseases (CVD), and lifestyle modification is the key to improving metabolic disorder. Diabetes mellitus has been shown to be a risk factor for coronary heart disease (CHD) and ischemic stroke in both Western and Japanese populations. An association between impaired fasting glucose and pre-hypertension found in an urban Japanese population emphasized the combined risk of CVD. Mean total cholesterol levels in Japan have been increasing in the last three decades. The Japanese evidence for the positive association of total cholesterol with CHD is similar to that in the West. Higher low-density lipoprotein cholesterol (LDL-C) levels pose an increased risk of CHD and atherothrombotic infarction, whereas lower LDL-C levels may pose an increased risk of intracerebral hemorrhage in Japan. Overall, the studies reviewed here show that impaired glucose metabolism and dyslipidemia are emerging risk factors for CVD in the Japanese population.

Keywords Impaired glucose metabolism · Dyslipidemia · Lifestyle · Predictors for cardiovascular disease · Cohort study · Japanese population

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Introduction

Metabolic syndrome comprises a cluster of components of impaired glucose metabolism, abdominal fat accumulation, dyslipidemia, and elevated blood pressure [1]. Each component has been shown to be an independent risk factor for cardiovascular diseases (CVD) in Japanese community cohort studies: impaired fasting glucose [2]; abdominal obesity [3, 4]; low-density lipoprotein cholesterol [5, 6]; and high-normal blood pressure [7–9].

Recently, a new streamlined definition of metabolic syndrome for global populations has been introduced [10]. In this definition, abdominal obesity is just one of the possible components for metabolic syndrome. However, in the Japanese definition of metabolic syndrome, abdominal obesity is an essential component [11]. The definition may mislead a prevention of CVD for non-obesity metabolic disorder, which is a modifiable risk factor for CVD. Changes in lifestyle are the key to improving metabolic disorder, including diabetes mellitus (DM) and dyslipidemia, and thereby to reducing the risk of cardiovascular disease. In this review paper, the focus is on the relation of metabolic symptoms, namely impaired glucose metabolism and dyslipidemia to CVD in the Japanese population.

Impaired glucose metabolism: trends, combination with blood pressure elevation, and individualized preventive approaches

Diabetes mellitus has become a major public health problem [12, 13] as well as a risk factor for mortality [12] and CVD

[14–16]. In Japan, the frequencies of hyperglycemia for 1961, 1974, and 1989 show a trend of increasing incidence: 12.1%, 13.8%, and 31.9% in men and 4.8%, 8.1%, and 27.2% in women, respectively [17].

Previous meta-analysis studies have shown that diabetes is a risk factor for ischemic stroke [18] and coronary artery disease [15, 18, 19]. The Framingham Offspring cohort study showed a positive relationship between impaired fasting glucose and coronary heart disease in women and between diabetes and coronary heart disease in men and women [20]. These results are compatible with those of previous cohort studies in Japan, as described below and summarized in Table 1.

The Hisayama Study indicated that diabetes as defined by the glucose tolerance test was a risk factor for ischemic stroke in men (hazard ratio 2.54; 95% confidence intervals 1.40 to 4.63) and women (hazard ratio 2.02; 95% confidence intervals 1.07 to 3.81) and coronary heart disease in women (hazard ratio 3.46; 95% confidence intervals 1.59 to 7.54) [21]; however, impaired glucose tolerance and impaired fasting glucose were not risk factors for ischemic stroke or coronary heart disease.

In a study of five communities in Japan, diabetes defined by non-fasting glucose levels was a risk factor for non-embolic ischemic stroke in men (hazard ratio 1.8; 95% confidence intervals 1.0 to 3.2) and women (hazard ratio 2.2; 95% confidence intervals 1.2 to 4.0) [22]. This result is similar to that of lacunar infarction. The risk was observed in both non-hypertensive subjects and obese subjects. The positive association was particularly strong in hypertensive subjects with higher skin-fold thickness values (hazard ratio 1.9 and 95% confidence intervals 1.0 to 3.7 for borderline diabetes; hazard ratio 4.9 and 95% confidence intervals 2.5 to 9.5 for diabetes).

A positive association between diabetes and CVD mortality was also observed in a Japanese general population. The

Table 1 Association between blood glucose categories and cardiovascular diseases in Japanese cohort studies

Study name	Number	Sex	Follow-up	End point	Results	Reference
The Suita Study	5321	MF	11.5	Stroke	DM, HR=2.08	[2]
				CHD	IFG, HR=1.46; DM, HR=2.28	
		M		Stroke	DM, HR=1.78	
		F		Stroke	DM, HR=2.66	
				CHD	IFG, HR=1.83; DM, HR=4.32	
The Hisayama Study	2421	M	14	CI	DM, HR=2.15; 2hPG, HR=2.71	[21]
		F		CI	DM, HR=2.10; 2hPG, HR=2.19	
				CHD	DM, HR=3.83; 2hPG, HR=4.44	
Five Japanese communities	4287	M	17	CI	DM, HR=1.8	[22]
				Lacunar infarction	DM, HR=2.1	
	6295	F	17	CI	DM, HR=2.2	
				Lacunar infarction	DM, HR=2.4	
	10582	MF	17	Non-embolic CI	Borderline with non-hypertension, HR=1.7	
					DM: with non-hypertension, HR=1.7	
					DM with higher BMI, HR=2.2	
JPHC study	31,192	MF	12.9	CHD	Borderline HR=1.5	[25]
					DM, HR=2.38	
NIPPON DATA80	9444	MF	17.3	All causes mortality	CBG>=11.1 mmol/L, HR=1.63	[23]
				CVD mortality	5.22 mmol/L<=CBG<7.77 mmol/L, HR=1.22	
					7.77 mmol/L<=CBG<11.1 mmol/L, HR=1.46	
					CBG>=11.1 mmol/L, HR=1.82	
				CHD mortality	7.77 mmol/L<=CBG<11.1 mmol/L, HR=2.43	
					CBG>=11.1 mmol/L, HR=2.62	
The Funagata Diabetes Study	2534	MF	5.7	All cause mortality	ADA 2007: DM, HR=2.11	[24]
				CVD mortality	WHO 1985: IGT, HR=2.3; DM, HR=3.54	
					ADA 2007: DM, HR=3.17	

M men; *F* women; *CHD* coronary heart disease; *CI* cerebral infarction; *CVD* cardiovascular diseases; *DM* diabetes mellitus; *IFG* impaired fasting glucose; *2hPG* 2 h post-loaded glucose levels; *HR* hazard ratio; *BMI* body mass index; *CBG* casual blood glucose; *ADA* American Diabetes Association; *WHO* World Health Organization.

NIPPON DATA 80 Study indicated that high and borderline-high casual blood glucose groups (11.1 mmol/L and 7.77 to 11.1 mmol/L, respectively) had increased risks of coronary heart disease mortality [23]. Similar results were observed for both CVD and all-cause mortality. The Funagata Diabetes Study showed that diabetes defined by both the WHO criteria (1985) and ADA recommendations (1997) were risk factors for all-cause mortality and cardiovascular mortality [24]. However, impaired fasting glucose was not a risk factor for all-cause mortality and cardiovascular mortality. These Japanese cohort studies for mortality risks indicated that diabetes is a risk factor for all-cause and CVD mortality. However, impaired fasting glucose and impaired glucose tolerance may not be risk factors for all-cause or CVD mortality. Further investigations of larger cohort studies are required to clarify these matters.

Recently, the Suita Study showed that impaired fasting glucose is a risk factor for the incidence of cardiovascular disease (hazard ratio 1.49; 95% confidence intervals 1.02 to 2.16) or coronary heart disease (hazard ratio 1.83; 95% confidence intervals 1.01 to 3.32) in women, and that diabetes is a risk factor for stroke in both men (hazard ratio 1.78; 95% confidence intervals 1.00 to 3.12) and women (hazard ratio 2.66; 95% confidence intervals 1.22 to 5.80) and for coronary heart disease in women (hazard ratio 1.78; 95% confidence intervals 1.00 to 3.12) [2]. In addition, compared with normoglycemic and optimal blood pressure Japanese subjects, increased risks of CVD were observed in normoglycemic subjects with high-normal blood pressure or hypertension, impaired fasting glucose subjects with normal or higher blood pressure, and diabetic subjects regardless of blood pressure category (Fig. 1: P-value for interaction=0.046). These two borderline categories may augment the risk of CVD.

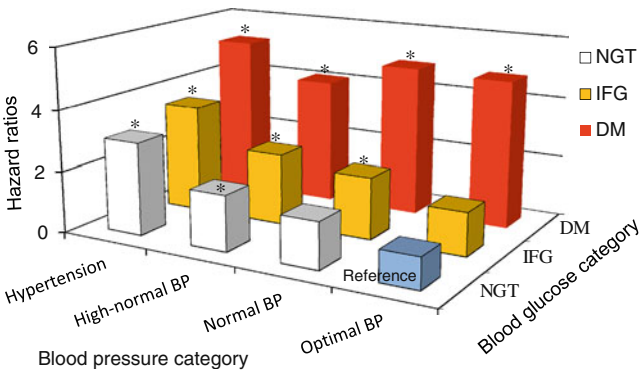

Fig. 1 Multivariable-adjusted hazard ratios of cardiovascular diseases according to the combination of blood pressure and glucose categories. Multivariable-adjusted hazard ratios were adjusting for age, sex, body mass index, smoking, drinking, and hyperlipidemia. *BP* blood pressure; *NGT* normal glycemic tolerance; *IFG* impaired fasting glucose; *DM* diabetes mellitus; *: $P<0.05$ (compared with the optimal blood pressure and normoglycemic group)

In a collaborative meta-analysis of 102 prospective studies from around the world, increased risks of coronary heart disease were observed in unknown diabetic subjects (i.e., subjects with diabetes who are not aware of their disease) with 5.6 to <6.1 mmol/L and 6.1 to <7 mmol/L (hazard ratios [95% confidence intervals]: 1.11 [1.04 to 1.18] and 1.17 [1.08 to 1.26], respectively) [18]. Quite recently, the Japan Public Health Center-based prospective (JPHC) study consisting of a 12.9-year of follow-up for 31,192 individuals aged 40–69 years was observed that diabetes mellitus and hyperglycemia carried an increased risk for coronary heart disease in a Japanese general population [25]. Based on this study and the Suita study [2, 25], both diabetes mellitus and impaired fasting glucose may be a risk factor for the incidence of coronary heart disease in Japan.

In the JPHC study's systematic review of the evidence for pre-diabetes, impaired fasting glucose and impaired glucose tolerance were shown to be associated with modest increases in the risk for CVD [25]. Overall relative risks (95% confidence intervals) for the association between two categories of impaired fasting glucose (100 to 125 mg/dL and 110 to 125 mg/dL) and CVD were 1.18 (1.09 to 1.28) and 1.20 (1.12 to 1.28), respectively. Meanwhile, the risks of CVD for impaired fasting glucose and impaired glucose tolerance were 1.10 (0.98 to 1.23) and 1.20 (1.07 to 1.34), respectively. In two Japanese cohort studies using the oral glucose tolerance test, impaired fasting glucose was not found to pose a risk of CVD [21, 24]. However, in one of these cohort studies, impaired glucose tolerance was observed as a risk of CVD mortality [24]. Larger Japanese cohort studies are required to establish the association between oral glucose tolerance test results and CVD.

In order to prevent CVD, a person with impaired glucose metabolism should eliminate or reduce other cardiovascular risk factors, such as high blood pressure, obesity, smoking, and excess drinking. The Suita study showed that the combination of impaired fasting glucose and high blood pressure greatly increased the risk of cardiovascular disease [2]. Recently, the frequencies of obesity in men and elderly women have increased in Japan [26]. Obesity is a risk factor for impaired glucose metabolism; weight loss reduces the risk of both impaired glucose metabolism [27] and CVD [3].

The average smoking rate in men worldwide has rapidly decreased in recent years, and in 2005 had dropped by 45.5% since its peak. However, the rate in Japan is still higher than that in Western countries [28]. And while, the smoking rate in women is generally lower than that in men. In Japan, the rate for younger women aged 20 to 39 years has increased to around 17 to 20% [28]. Smoking itself is a risk factor for diabetes mellitus [29]. Smoking cessation reduces the risk of both diabetes mellitus [30] and CVD

[31]. Excess drinking is a risk factor for increasing blood pressure [32] and stroke [33]. In order to reduce the risk of CVD, subjects with a combination of two borderline risks, high-normal blood pressure and hyperglycemia, should modify their lifestyles, aiming at cessation of smoking and even moderate drinking, as well as weight reduction if there are overweight or obese.

Dyslipidemia: risks, trends, and individual treatment approaches

According to Japan's National Survey on Circulatory Disorders in 1980, 1990, and 2000, mean levels of total cholesterol increased from 186 mg/dL and 191 mg/dL in 1980 to 200 mg/dL and 208 mg/dL in 2000 among adult men and women, respectively. Frequencies of hypercholesterolemia (total cholesterol levels of 220 mg/dL or more) increased 15% and 19% in 1980 to 27% and 35% in 2000 among men and women, respectively [34]. The difference in mean total cholesterol levels between Japanese and American men was approximately 40 mg/dL in the 1980s. However, this difference had diminished to 15 mg/dL by 1990 and 2000. No changes in mean total cholesterol levels in Japanese or American men aged 60 years and over were observed from 1990 to 2000 [28].

Total cholesterol

A previous meta-analytic study has shown that total cholesterol was positively associated with ischemic heart disease in both middle and old age and at all blood pressure categories [35]. In contrast, the association between total cholesterol and the risk of stroke remains unclear. The Multiple Risk Factor Intervention trial has shown that the risk of death from intracerebral hemorrhage was three times higher in men with serum cholesterol levels under 160 mg/dL than in those with higher cholesterol levels, whereas a positive association was observed between the serum cholesterol level and death from ischemic stroke [36]. A meta-analysis of 45 prospective cohort studies showed no association between blood cholesterol levels and stroke except in those under 45 years of age when screened [37]. The inconsistency in results may be due to the different etiologic origins of stroke. Dyslipidemia may be important for some subtypes of stroke but not for others, because stroke is a heterogeneous disease of various etiologic origins. In American men, an inverse association was observed between the total cholesterol levels and the incidence of intracerebral hemorrhage, while a positive association was observed between total cholesterol levels and the incidence of cerebral infarction [36].

Japanese cohort studies have shown evidence of the positive association of total cholesterol with coronary heart disease similar to that in Western studies. NIPPON DATA80 showed associations between total cholesterol and risk of all-cause mortality (hazard ratio 1.19 and 1.36; 95% confidence intervals, 1.03 to 1.37 and 1.05 to 1.77) in both the lowest (<160 mg/dl) and highest (≥260 mg/dl) total cholesterol groups, respectively [38]. In addition, the hazard ratios of coronary heart disease mortality were 1.4 in the 200 to 219 mg/dL total cholesterol group, 1.7 in the 220 to 239 mg/dL group, 1.8 in the 240 to 259 mg/dL groups, and 3.8 in the 260 mg/dL or above group, compared with the 160 to 179 mg/dL total cholesterol (healthy control) group [38].

LDL cholesterol and non-HDL cholesterol

The Suita Study showed a positive association between serum low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (non-HDL) cholesterol levels and increased incidence of myocardial infarction, but not with any type of stroke [6]. The hazard ratio for myocardial infarction was highest in the top quintile of LDL cholesterol (hazard ratio, 3.03; 95% confidence intervals, 1.32 to 6.96) when men and women were combined. The hazard ratio for myocardial infarction was also highest in the top quintile of non-HDL cholesterol (hazard ratio, 2.97; 95% confidence intervals, 1.26 to 6.97). There was no substantial difference in the predictive value for the incidence of myocardial infarction between LDL cholesterol and non-HDL cholesterol. LDL cholesterol can be calculated from fasting blood sample and measurement of total cholesterol, HDL cholesterol, and triglyceride levels from fasting blood samples, according to the Friedewald formula [39]. The formula is not applicable for serum triglyceride levels equal to or greater than ≥400 mg/dL. However, non-HDL cholesterol levels can be easily calculated by routine measured parameters, total and HDL cholesterol without the effect of non-fasting status or hypertriglyceridemia (≥400 mg/dL).

The Hisayama Study showed that the positive association between LDL cholesterol levels and risk of atherothrombotic infarction (P for trend=0.02) and coronary heart disease (P for trend=0.03) remained significant after multivariable adjustment. In the Ibaraki Prefectural Health Study, which was a very large sample consisting of 30,802 men and 60,417 women, high LDL cholesterol levels were associated with an increased risk of mortality from coronary heart disease in men, but not in women [40]. The same study showed that lower LDL cholesterol levels are associated with elevated risk of mortality from intracerebral hemorrhage, but are not associated with increasing risk of cerebral infarction [41]. These Japanese cohort studies suggest that higher levels

of LDL cholesterol pose an increased risk of coronary heart disease and possibly atherothrombotic infarction, whereas lower levels of LDL cholesterol may increase the risk of intracerebral hemorrhage.

Recently, the lectin-like oxidized LDL receptor 1 (LOX-1) has been implicated in atherothrombotic diseases [42]. Activation of LOX-1 in humans can be evaluated by use of the LOX index, obtained by multiplying the circulating concentration of LOX-1 ligands containing apolipoprotein B by that of the soluble form of LOX-1. In the Suita Study, higher LOX index values were associated with an increased risk of coronary heart disease [43].

HDL cholesterol

Lower HDL cholesterol predicts coronary heart disease mortality and occurrence of new coronary heart disease events [44]. Elevated total cholesterol was not found to be associated with coronary heart disease mortality in older men, but may be a risk factor for coronary heart disease in older women [44]. The Israeli Ischemic Heart Disease Study showed an independent negative association between HDL cholesterol and ischemic stroke mortality during 21 years of follow-up [45].

Among the Japanese cohort studies, the Oyabe Study demonstrated that lower HDL cholesterol levels were related significantly and independently to an increased risk of all-stroke incidence and ischemic stroke incidence [46]. And in a combined prospective cohort study of 13 urban industrial companies, coronary heart disease incidence was inversely related to HDL cholesterol in Japanese men [47].

Triglyceride

Based on combined data from prospective studies, a high serum triglyceride level is a risk factor for CVD for both men (hazard ratio, 1.32; 95% confidence intervals, 1.26 to 1.39) and women (hazard ratio, 1.76; 95% confidence intervals, 1.50 to 2.07) in the general population, independent of HDL cholesterol [48]. In 26 prospective studies in Asian and Pacific populations, serum triglycerides were an independent predictor of coronary heart disease and stroke risk [49]. In 29 prospective meta-analytic studies in the West, triglyceride levels were moderately associated with coronary heart disease [50].

In Japanese cohort studies, two studies have provided evidence regarding the association between serum triglyceride levels and coronary heart disease and ischemic stroke. A cohort study of four rural communities showed that a high serum triglyceride level was a risk factor for coronary heart disease; even after adjustment for HDL cholesterol levels the significant association remained, although 80% of the baseline participants were non-fasting [51]. The Suita Study has also shown that the risk for ischemic stroke was highest in participants with high triglycerides alone, and that a combination of high serum levels of triglyceride and non-HDL cholesterol was associated with an increased risk of myocardial infarction [52]. High serum levels of triglyceride and non-HDL cholesterol are both important targets for the prevention of CVD, which requires evidence-based guidelines for management in the primary care setting.

Concluding remarks and outlook

This paper reviews the associations of impaired glucose metabolism and dyslipidemia with CVD in Japanese cohort studies. Diabetes mellitus is a risk factor for coronary heart disease and ischemic stroke. Impaired fasting glucose and high-normal blood pressure were shown to be independent risk factors for CVD and coronary heart disease in an urban cohort. The combination of these two borderline categories may increase the risk for CVD. Impaired glucose tolerance has not been observed as a risk factor for the incidence of CVD in Japan. The Japanese evidence for the positive association of total cholesterol with coronary heart disease is similar to that of previous Western studies. Associations with all-cause mortality were observed for both the lower and higher levels of cholesterol: Higher levels of LDL cholesterol have been shown to increase the risk of coronary heart disease and atherothrombotic infarction, whereas lower levels of LDL cholesterol may increase the risk of intracerebral hemorrhage in Japan, as elsewhere. HDL cholesterol levels were inversely related with ischemic stroke. Positive associations between serum triglyceride levels and coronary heart disease and ischemic stroke have also been observed in Japanese populations. The Japanese diet has been rapidly changing in recent decades, as reflected in many of its health indicators such as cholesterol levels, and both impaired glucose metabolism and dyslipidemia are emerging as important risk factors for CVD in the Japanese population. In order to reduce the risk of CVD, subjects with metabolic disorder should reduce other cardiovascular risk factors and improve their lifestyle.

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