The Epidemiology of Diabetes in Korea: From the Economics to Genetics

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To determine the factors responsible for the dramatic increase in the prevalence of diabetes in Korea. A computerized literature survey was conducted to evaluate the risk factors for Type 2 diabetes mellitus (T2DM) in Korea, including genome-wide association studies. National Statistics gross national income data was integrated with the reported prevalence of diabetes to evaluate the relationship between diabetes and the economic growth. The strength of the association was evaluated using measures of effect size, such as odds ratio and relative risks. The putative risk factors identified in Korean studies are very similar to the risk factors identified from the other countries, including genetic background. Genome-wide association studies reported relative risks of 1.5 or less, indicating that no single gene is associated with the risk of T2DM. The scientific evidence suggests that the dramatic increase in the incidence and prevalence of T2DM in Korea is related to the economic development of Korea, which has a direct influence on health policy, as well as an individual's health behaviors. We expect to observe the current diabetes incidence rates until the key risk factors are present for long enough in our society, at which point we would expect to start observing a more gradual increase in both the incidence and prevalence of T2DM in Korea.

Keywords: Epidemiology; Economy; Genetics

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major health problem affecting more than 170 million people worldwide, with a major increase expected in Asia in the next 20 years, as indicated by the predicted doubling of the diabetic populations in India and China [1]. In the USA, more than 13% of adults over the age of 20 years have been diagnosed with T2DM [2]. T2DM is also a major chronic disease and public health problem in Korea. The prevalence of diabetes mellitus in Korea increased from less than 1% in 1960 to 6-9% by the end of the 1990s [3,4]. The rapid rise in the prevalence of diabetes and cardiovascular disease in Korea may be related to an increasingly Westernized diet, decreased physical activity, an increasing obese population, and genetic background [5]. The putative risk factors for T2DM in the Korean population include (but are not limited to) increasing age, urban living, female gender, obesity, smoking, family history of diabetes, impaired liver function, metabolic syndrome, elevated blood pressure, and increased triglycerides. For a better understanding of T2DM in Korea, the magnitude of the prevalence, incidence, and risk factors still needs to be evaluated.

The most recent report from a large size community cohort prospective study revealed the age, gender, and resident specific annual incidence of T2DM was 1.33%, 1.55%, 1.68%, and 2.35% in 40-year-old rural female, urban female, rural male, and urban male, respectively. In 50-year-old the rate increased to 1.48% in rural female, 1.65% in rural male, 2.3% in urban female, and 3.18% in urban male. In 60-year-old, 1.85% in rural male, 2.05% in rural female, 4.1% in urban female, and 4.55% in urban male. In 70-year-old, the rate increased to 3.08% in rural female, 3.93%...
in rural male, 5% in urban female, and 5% in urban male. The incidence rates stratified by age and gender in rural subjects showed ‘J’ shaped pattern, but linear pattern was observed in urban subjects.

The prevalence of T2DM was 5.2%, 5.4%, 7.5%, and 10% in 40-year-old urban women, rural women, rural men, and urban men, respectively. In 50-year-old, the prevalence increased to 10.9% in urban women, 13.5% in rural women, 14.9% in rural men, and 16.5% in urban men. In 60-year-old, the prevalence was 16.5% in rural men, 17.5% in rural women, 17.5% in urban women, and 24.8% in urban men. A relatively higher prevalence was observed in the urban and male populations [6].

ECONOMY AND DIABETES

Korea has experienced a dramatic increase in the prevalence of diabetes since the early 1990s; however, the rapid increase in the prevalence of chronic disease could be the result of various artifacts, rather than being the consequence of risk factors. The artifacts responsible for dramatic changes of the prevalence and incidence of chronic disease in Korea include:

1) Changes in diagnostic methods and criteria,
2) Changes in national health policy and the health insurance system,
3) Promotion of disease awareness, and
4) A sudden change or increased exposure to key risk factors.

However, it is almost impossible for exposure of a large population to a key risk factor to result in a such dramatic increasing pattern of chronic diseases. For example, chronic diseases, such as diabetes, are the consequence of exposure to multiple risk factors over a long period of time. In other words, exposure to multiple risk factors from the environment, lifestyle, and habitual factors results in the progression of disease at different rates among individuals and in a gradual pattern. Therefore, the onset of diabetes occurs based on the individual’s susceptibility, immunity, and exposure amount, as well as on the duration of the risk factors and incubation period. Thus, the dramatic change in the patterns of incidence and prevalence of diabetes are related to economic changes of individual nations, as well as the individual’s health behavior.

As shown in Fig. 1, Korea has experienced both steady economic growth and an increasing prevalence of diabetes. In the early 1970s, epidemiologic studies from Korea reported a T2DM prevalence of less than 2%; however, a log linear increase in prevalence was observed, starting in 1987. This is an unusual pattern if the prevalence is the result of the risk exposure, as one would expect a gradual linear increase if the prevalence is related to risk exposure. The Korean government implemented a universal health insurance system in 1987, and the prevalence of diabetes clearly reflects a “seeking of disease” concept. This hypothesis is further supported by the fact that the Korean gross national income is curtailing the prevalence pattern of diabetes (Fig. 1). Diabetes awareness campaigns, individuals’ health care attitudes and interest, screening programs, and national health care coverage are relate to the higher prevalence of diabetes and contribute to the logarithmic prevalence pattern. The most recent study from the National Health Insurance Corporation and the Bureau of National Statistics indicated a total of 2 million people with diabetes in Korea [7]. However, this report did not include asymptomatic cases, which are present in about the same amount as known cases. If we include asymptomatic cases, as well as impaired glucose tolerance cases, we would estimate somewhere around 4-5 million people with T2DM or at high risk for T2DM in Korea [8].

We suggested that the rapid rise in both incidence and prevalence of diabetes in Korea is largely due to national health policy; however, to some degree, the rise is due to exposure to multiple risk factors. Thus, let us evaluate the risk factors of the T2DM in Korea and the magnitude of these risk factors.

RISK FACTORS

The putative risk factors for T2DM in the Korean population include (but are not limited to) old age, urban living, female gender, obesity, smoking, family history of diabetes, impaired liver function, metabolic syndrome, elevated blood pressure, and increased triglycerides. Although some risk factors have yet to be identified, the aforementioned variables are the key risk factors for diabetes mellitus in Koreans. Most of these risk factors have also been identified as key risk factors in other locations, including Europe, South and North America, and Africa. Moreover, seventy percent of identified risk factors are modifiable. For example, smoking is a habitual behavior and is modifiable. Several prospective studies have demonstrated the risk association between cigarette smoking and diabetes in both Caucasian and Asian populations [9-14]. In the 21,068-participant U.S. Physicians’ Health Study, both former and current smokers had an increased risk of self-reported diabetes in a
dose-response relationship. Similarly, in the Nurses’ Health Study, a dose-dependent relationship between smoking and diabetes incidence among 114,247 female nurses had been reported [15]. Although these dose-relationships were not always consistent, this may be due to differences in study design, participant characteristics, and measurement methods [10,16,17].

In a study from Korea, smokers (ex- and current) had a higher incidence of diabetes mellitus than never-smokers (6.3% vs. 5.1%, \( P < 0.05 \)). The incidence of diabetes was 5.1%, 8.3%, 5.1%, and 6.8% in never-smokers, ex-smokers, current smokers, and heavy smokers, respectively (\( P < 0.05 \)). In this study, compared to never smokers, the ex- and heavy smokers had a 2-fold increased risk of diabetes, while current smokers had a 1.5-fold increased risk. Furthermore, the population attributable risk of smoking for diabetes was 14% (95% confidence interval [CI], 4.4% to 23.6%) [18]. In other words, if no smokers were present in Korea, then 14% of the cases of diabetes could be prevented. In addition, urban living, obesity, impaired liver function, metabolic syndrome, elevated blood pressure, and increased triglycerides are all modifiable risk factors and all independently contribute to the risk of diabetes. The relationship between liver function and T2DM has been investigated in numerous clinical and epidemiologic studies. In a study in Korea, ALT levels had a dose-dependent effect on the prevalence of T2DM at baseline examination from 3.2%, 4.1%, 6.3%, and 12.5% (\( \chi^2 = 256.8; P < 0.001 \)) in lowest to highest quartile groups, respectively. However, at the follow-up evaluation, the incidence of T2DM was 2.5%, 2.3%, 4.0%, and 7.1% for the respective quartile groups. The relative risks were 0.9 (95% CI, 0.55 to 1.53; \( P = \text{ns} \)), 1.67 (1.06 to 2.6; \( P < 0.05 \)), and 3 (1.97 to 4.7; \( P < 0.001 \)), when compared to the lowest quartile group. Furthermore, a multiple logistic regression analysis revealed that age-adjusted relative risk was 1.34 (95% CI, 0.98 to 1.85; \( P = 0.07 \)) in the 2nd quartile, 1.91 (1.41 to 2.59; \( P < 0.001 \)) in the 3rd quartile, and 2.95 (2.17 to 4.0; \( P < 0.001 \)) in the 4th quartile group, when compared to the lowest quartile group [19].

The rise of diabetes incidence and prevalence in Korea is a result of both health policy change and exposure to putative risk factors. In the past 10 years, genetic susceptibility has emerged as a new key risk factor for T2DM. We will now evaluate the strength of genetics as a risk factor of T2DM.

**GENETICS AND DIABETES**

The genome-wide association (GWA) approach is an emerging methodology that enables us to identify genetic variants with
specific loci predisposing individuals to complex traits and diseases [20]. Several genes identified through linkage scans or the candidate gene approach have been confirmed to be associated with T2DM (e.g., PPARG, KCNJ11, HNF4A, and CAPN10). Furthermore, under the common variant-common disease hypothesis, several GWA studies on T2DM have been conducted in large-scale case-control samples. Seven novel genes (TCF7L2, SLC30A8, HHEX, CDKAL1, CDKN2A and CDKN2B, IGF2BP2, and FTO) have been reproducibly demonstrated to have a modest association with T2DM (odds ratio [OR], 1.12 to 1.37) in multiple populations of European ancestry [21-25]. While many of the genes are implicated in the insulin production/secreption pathway (TCF7L2, SLC30A8, HHEX, CDKAL1, CDKN2A/B and IGF2BP2), FTO is associated with T2DM through its regulation of adiposity [25,26]. Moreover, a region near CDKN2A/B is associated with risk of both T2DM and cardiovascular diseases [27,28]. Despite consistent associations among Europeans, the contributions of these genetic variants in other ethnic groups are unclear. Given the differences in environmental factors (e.g., lifestyle), risk factor profiles (body composition and insulin secretion/resistance patterns), and genetic background (linkage disequilibrium pattern and risk allele frequencies) between Europeans and Asians, it is important to understand the role of these genes in Asians.

Recent GWA studies have been performed in a Chinese population in Hong Kong (involving 6,795 T2DM cases and non-diabetic controls) and two Korean populations. The risk alleles were consistent among the three Asian populations and were consistent with those reported in Europeans [21-25]. TCF7L2 (rs7903146) showed the strongest effect (OR, 1.34), followed by CDKN2A/B (rs10811661), CDKAL1 (rs7754840 and rs7756992), HHEX (rs1111875, rs5015480 and rs7923837), SLC30A8 (rs13266634), IGF2BP2 (rs4402960), and FTO (rs8050136). Haplotype analyses did not reveal a more significant association than single-marker analyses. Interestingly, multiple single nucleotide polymorphisms at CDKAL1 and HHEX were significantly associated with T2DM risk. However, only rs10811661 near CDKN2A/B was highly significant for association with T2DM.

Since the reported T2DM genes may be implicated in different metabolic pathways, subset analyses were performed by dividing the T2DM patients into non-obese (body mass index [BMI] <25 kg/m²) and obese subgroups using the Asian guideline for the definition of obesity [28]. The study found that the associations for T2DM were significantly higher in the non-obese subgroup, as compared to the obese subgroup in the combined samples for CDKAL1 (rs7754840) and CDKN2A/B (rs10811661) (OR, 1.29 vs. 1.15 and 1.39 vs. 1.20 in non-obese and obese subgroups, respectively, heterogeneity = 0.05). The former association in non-obese diabetes was also observed in an Icelandic population [24]. On the other hand, FTO showed a stronger association in the obese subgroup (OR, 1.06 vs. 1.27 in non-obese vs. obese subgroups, heterogeneity = 0.05). The result for FTO is consistent with the finding that the T2DM association was lost after adjustment for BMI (OR, 1.18; P = 0.126 before and after adjustment for BMI, respectively). Moreover, the risk allele of FTO was highly associated with increased BMI in the combined samples (P = 1.7×10⁻⁶). Taken together, FTO alters the risk for T2DM, primarily through effects on adiposity, which is consistent with reported findings in Europeans [25,26,29]. In addition to BMI, the risk alleles for SLC30A8 (rs13266634) and HHEX (rs1111875) were significantly associated with diagnosis at an earlier age [30].

These studies provide important insight into the impact of the new T2DM genes identified through genome-wide association studies. However, the strength of the effect size is not as strong as some of the risk factors, such as family history of diabetes. Therefore, we are inclined to believe that the link between diabetes and genetic susceptibility is genuine, but, however, is not a key risk factor for T2DM.

**SUMMARY**

Numerous epidemiologic studies from Korea have revealed a high rate of diabetes. Although the effect sizes are different, the putative risk factors identified from Korean studies are very similar to the risk factors identified from the other countries. Furthermore, the genes identified through genome-wide association studies conducted in both Asian and Caucasian populations revealed a lower effect size. These genetic studies reported a relative risk of 1.5 or less, indicating that no single gene is associated with the risk of T2DM; however, a strong interaction between genetic factors and lifestyle, diet, and habitual factors was suggested. In addition, relative risk (RR) and OR are statistics that only describe an association, not causation. RR and OR also refer to a population and not to an individual patient. Furthermore, studies of small groups are more likely to find an association that might actually be due to chance, while larger groups are less likely to show an association between a risk factor and an outcome. Finally, when the incidence of an outcome
of interest in the study population is low (<10%), the OR is close to the RR; the more frequent the outcome becomes, the more the OR will overestimate the RR when OR is greater than 1 or underestimate the RR when OR is less than 1.

In conclusion, the high incidence and prevalence of T2DM in Korea is related to economic development, which has a direct influence on health policy, as well as an individual's health behaviors, and which is associated with a high rate of T2DM. Environmental and genetic factors very likely contribute to some degree to the high rate of diabetes in Korea. Finally, although genetic factors are independently associated with an onset of T2DM, the strength of an association is less than that of the environmental risk factors that have been reported. Therefore, we expect to observe the current diabetes rates until the key risk factors incubate long enough in our society, at which point we would expect to start observing a more gradual increase in both the incidence and prevalence of T2DM in Korea.

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