

## **Insulin Secretion and Insulin Resistance in Newly Diagnosed, Drug Naive Prediabetes and Type 2 Diabetes Patients With/Without Metabolic Syndrome**

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### **Introduction**

The pathogenesis of diabetes is complicated by several metabolism-related problems. In particular, a deterioration in insulin secretion and an aggravation of insulin resistance are known to be essentials in the primary pathogenesis of type 2 diabetes mellitus (DM) [1]. In terms of insulin resistance, type 2 DM and metabolic syndrome (MS) are closely related. The Botnia study showed that 84% of men and 78% of women with type 2 DM had accompanying MS. For patients with prediabetes, 64% of men and 42% of women had MS, and for normal glucose tolerance (NGT) groups, only 15% of men and 10% of women had MS [2]. However, not all type 2 DM patients have MS and neither do all MS patients have accompanying type 2 DM. This signifies that even though these two diseases have much in common, that they differ pathophysiologically. For these reasons, we undertook this study to compare differences in type 2 DM according to the co-existence of MS with respect to insulin secretion and insulin resistance. To exclude the effect of artificial intervention or severe  $\beta$ -cell dysfunction, the subjects enrolled in this study were confined to newly diagnosed and drug naive.

### **Subjects and Methods**

#### **SUBJECTS**

This study was carried out on 322 subjects suspected of having type 2 DM. In order to avoid severe  $\beta$ -cell dysfunction and to exclude any change in insulin secretory function or insulin resistance due to artificial intervention, study subjects were confined to having a history of hyperglycemia of less than three months and no history of taking a medication that might affect glucose metabolism.

#### **METHODS**

To diagnose type 2 DM, we used oral glucose tolerance test (OGTT). Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, and HbA1c were measured before carrying out OGTT.

According to OGTT results, subject were divided into three groups: a normal glucose tolerance (NGT) group, a prediabetes (preDM) group, comprised of an impaired fasting glucose (IFG) group and/or an impaired glucose tolerance (IGT) group, and a type 2 diabetes mellitus (T2DM) group. And, HOMA-IR (the insulin resistance index)

and IGI (insulinogenic index, which means the insulin secretion ability index) were calculated for all subjects who underwent OGTT [3].

$$\mathbf{HOMA-IR = (Ins_0 \times Glc_0)/22.5}$$

$$\mathbf{IGI = (Ins_{30} - Ins_0) / 18 (Glc_{30} - Glc_0)}$$

Ins0: fasting plasma insulin (mIU/L)

Ins30: insulin 30 minutes after glucose intake (mIU/L)

Glc0: fasting plasma glucose (mmol/L)

Glc30: plasma glucose 30 minutes after glucose intake (mmol/L)

Study subjects were stratified according to the presence of MS and were diagnosed according to adult treatment panel (ATP) III diagnostic criteria of MS of the National Cholesterol Education Program (NCEP) by using basic anthropometric data, OGTT results, and lipid profiles [4]. However, for MS diagnosis, abdominal circumference thresholds were taken as 90 cm for men and 80 cm for women, according to the Asian-Pacific abdominal obesity guidelines [5]. By using the indices mentioned above, the three subject groups were subdivided into 6 subgroups; i.e. NGT, preDM, and T2DM, each with/without MS. The clinical characteristics, insulin secretory functions, and insulin resistances of these subgroups were compared.

## **Results**

### CLINICAL CHARACTERISTICS OF THE STUDY SUBJECTS

According to OGTT results, 63 subjects were diagnosed with normal glucose tolerance, 81 subjects with impaired fasting blood glucose and/or impaired glucose tolerance and 178 with type 2 DM. According to ATP III criteria modified in-line with the Asian-Pacific guidelines, 218 subjects (67.7% of total) were diagnosed with MS. When subjects in the three main groups were compared, 34.9% of the NGT group had MS, whereas 60.5% of the prediabetes group, and 82.6% of the type 2 DM group had MS (Figure 1).

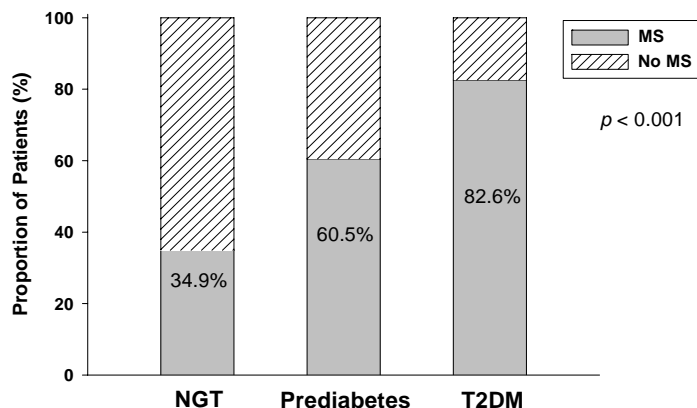


Figure 1. Prevalence of Metabolic syndrome among study subjects

#### COMPARISONS OF HOMA-IR AND IGI ACCORDING TO GLUCOSE TOLERANCE AND METABOLIC SYNDROME

On comparing the 3 groups stratified by the presence of MS, mean HOMA-IR and IGI were higher in those with MS. However, in the case of the prediabetes and type 2 DM groups those with MS, showed significantly higher HOMA-IR and IGI values than those without, whereas in the NGT subgroup, HOMA-IR and IGI levels were not dependent on the presence of MS.

When the three groups were subdivided according to the presence of MS and examined with respect to glucose tolerance, the NGT, preDM, and type 2 DM subgroups in MS group showed significant higher HOMA-IR and lower IGI according to glucose tolerance. On the other hand, the NGT, preDM, and type 2 DM subgroups in non-MS group showed a significant decrease in IGI but no significant difference in HOMA-IR as glucose tolerance worsened.

#### Conclusion

These findings suggest that deterioration in IGI and aggravation of HOMA-IR are both important in the primary pathogenesis of diabetes in those with MS. However, IGI deterioration may be the only important factor in the primary pathogenesis of T2DM in the absence of MS. Even though their proportions are relatively small, there exist type 2 DM patients whose disease cannot be explained by the current pathogenic theory - compensatory insulin deterioration against a background of insulin resistance aggravation (Figure 2).

Prospective studies that overcome the present study's limitations, comparative studies between races, and work at the molecular level would empower us to present a

clearer view of the comparative characteristics, relationships, and pathophysiologies of MS and early stage type 2 DM.

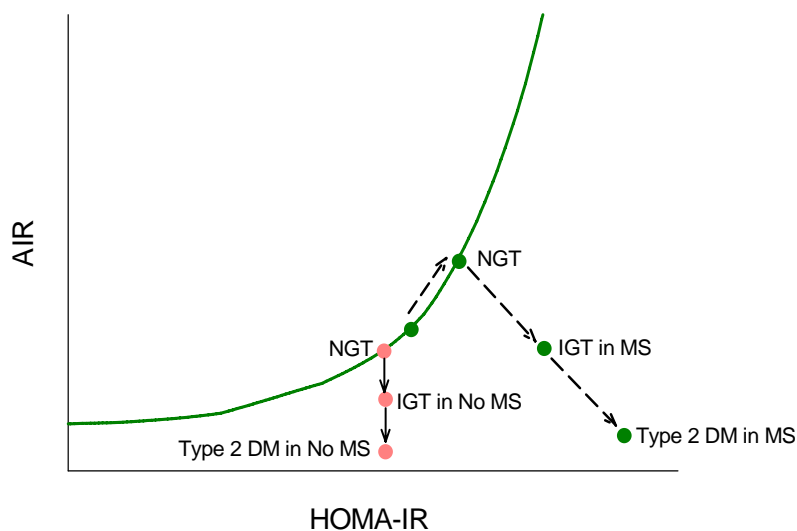


Figure 2. Hypothesis concerning primary metabolic changes during the development of type 2 DM. In patients with MS, IGI (compensatory insulin secretion) deterioration and HOMA-IR (insulin resistance) aggravation are both important in the primary pathogenesis of diabetes. However, HOMA-IR aggravation may not be an important factor in the pathogenesis of diabetes in those without MS.

### Acknowledgement

This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (Grant No. A050463).

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