Combined Influence of Insulin Resistance, Overweight/Obesity, and Fatty Liver as Risk Factors for Type 2 Diabetes

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OBJECTIVE—There is dissociation between insulin resistance, overweight/obesity, and fatty liver as risk factors for type 2 diabetes, suggesting that different mechanisms are involved. Our aim was to *1*) quantify risk of incident diabetes at follow-up with different combinations of these risk factors at baseline and *2*) determine whether each is an independent risk factor for diabetes.

RESEARCH DESIGN AND METHODS—We examined 12,853 subjects without diabetes from a South Korean occupational cohort, and insulin resistance (IR) (homeostasis model assessment-IR ≥75th centile, ≥2.0), fatty liver (defined by standard ultrasound criteria), and overweight/obesity (BMI ≥25 kg/m^2) identified at baseline. Odds ratios (ORs) and 95% confidence intervals (CIs) for incident diabetes at 5-year follow-up were estimated using logistic regression.

RESULTS—We identified 223 incident cases of diabetes from which 26 subjects had none of the three risk factors, 37 had one, 56 had two, and 104 had three. In the fully adjusted model, the OR and CI for diabetes were 3.92 (2.86–5.37) for IR, 1.62 (1.17–2.24) for overweight/obesity, and 2.42 (1.74–3.36) for fatty liver. The OR for the presence of all three factors in a fully adjusted model was 14.13 (8.99–22.21).

CONCLUSIONS—The clustering of IR, overweight/obesity, and fatty liver is common and markedly increases the odds of developing type 2 diabetes, but these factors also have effects independently of each other and of confounding factors. The data suggest that treatment for each factor is needed to decrease risk of type 2 diabetes.

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People who develop type 2 diabetes represent a heterogeneous group of individuals, some of whom have normal insulin sensitivity, normal weight, and β-cell failure; others have insulin resistance (IR) and inadequate compensatory hyperinsulinemia; and others have a combination of defects in both insulin sensitivity and β-cell function (1,2). The prevalence of diabetes is predicted to double between the years 2000 and 2030 (3) and, although an ageing population and increasing urbanization in developing countries will contribute to this marked increase in prevalence (3), the predicted prevalence is likely to be underestimated because of the increasing global burden of obesity. Several potential mechanisms may explain why obesity is a strong risk factor for diabetes (4). These mechanisms include increased production of nonesterfied fatty acids; adipokines/cytokines, including tumor necrosis factor-α, resistin, and retinol-binding protein 4; as well as reduced levels of adiponectin and mitochondrial dysfunction that compromise β-cell function (5). Although obesity has undoubtedly contributed to the burden of diabetes (4) and strategies to decrease body fat are effective in decreasing risk of diabetes, there are several unanswered questions regarding the mechanism(s) of the link between obesity and diabetes (5).

IR is also a risk factor for type 2 diabetes (6,7) and has a close association with obesity. Both obesity and IR are also strongly associated with fatty liver (8,9), and it is now evident that fatty liver is a risk factor for type 2 diabetes (10–13). However, fatty liver may occur in both normal weight and overweight/obese individuals, and the precise mechanism by which fatty liver increases risk of type 2 diabetes is uncertain. Fatty liver may affect risk of diabetes via an effect on the secretion of hepatokines (14), increased gluconeogenesis, decreased glycogen synthesis, and inhibition of insulin signaling (15,16). Although fatty liver is associated with diabetes, not all individuals with fatty liver have IR (17–19). Thus, although IR, overweight/obesity, and fatty liver are strongly correlated, there is clear evidence of dissociation between these three risk factors. The dissociation between these risk factors suggests that different pathogenetic mechanisms may operate by which insulin resistance, overweight/obesity, and fatty liver contribute to type 2 diabetes. Affected individuals who develop type 2 diabetes may have any one, two, or three of these risk factors, but the impact of different combinations of risk factors is uncertain. Establishing the roles of the different combinations of these risk factors may be helpful to understand the pathogenesis of type 2 diabetes and to inform approaches to prevention and treatment. Using data from a cohort study with measurements of IR, overweight/obesity, and fatty liver at baseline, the aim of our study was to *1*) estimate the strength of the association

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between different combinations of these three risk factors and incident diabetes and 2) determine whether the effects of each factor are independent of each other and potential confounding factors.

RESEARCH DESIGN AND METHODS

Study subjects

The study population consisted of individuals who had a comprehensive health examination at baseline (2003) and were reexamined 5 years later (2008) at Kangbuk Samsung Hospital, College of Medicine, Sungkyunkwan University, South Korea. Initially 15,638 participants were identified and 416 were excluded for having type 2 diabetes at baseline (based on any one or more of self-reported, medical histories and fasting plasma glucose results). Individuals with data missing at baseline for the following variables were also excluded: plasma glucose (n = 1), serum insulin (n = 1,346), BMI (n = 26), alcohol consumption (n = 399), smoking (n = 361), education (n = 581), and exercise (n = 309). After all the exclusions, 12,853 participants were eligible for this analysis from which 223 participants were diagnosed with diabetes by 2008. The study was approved by the Institutional Review Board at Kangbuk Samsung Hospital. Informed consent was not required because personal identifying information was not used.

Measurements and calculations

The health examination included full medical histories, physical examinations, and blood samples. BMI was calculated as weight in kilograms divided by height in meters squared. Questionnaires were used to ascertain information regarding alcohol consumption (g/day), smoking (never, ex-, current), duration of education (school ≤12 years, college 13–14 years, university >14 years), and frequency of exercise (none, less than once a week, at least once a week).

Blood samples for laboratory examinations were collected after an overnight fast. Fasting plasma glucose, total cholesterol, triglyceride, and HDL cholesterol concentrations were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). LDL cholesterol concentration was calculated using the Friedwald equation. Insulin concentration was measured with an immunoradiometric assay (Biosource, Nivelle, Belgium) with an intra- and interassay coefficient of variation of 2.1–4.5% and 4.7–12.2%, respectively. Homeostasis model assessment (HOMA) index was calculated by the following equation (HOMA-IR = [fasting insulin (μIU/mL) × fasting glucose (mmol/L)]/22.5). Since there are no population-specific thresholds to indicate IR in a Korean population, we stratified the populations using the 75th centile to establish an insulin-resistant group (HOMA-IR ≥75th centile), which was compared with a more insulin-sensitive group (HOMA-IR <75th centile). BMI ≥25 kg/m^2 was used to define overweight/obesity. Abdominal ultrasonography (Logic Q700 MR; General Electric, Milwaukee, WI) using a 3.5-MHz probe was performed in all subjects by experienced clinical radiologists, and fatty liver was diagnosed based on standard criteria, including hepatorenal echo contrast, liver brightness, and vascular blurring (20).

Statistical analysis

Continuous variables were expressed as mean ± SD for normally distributed variables or median (interquartile range) if not normally distributed. Continuous variables were compared using independent t tests, non-normally distributed variables were compared using Mann-Whitney U tests, and categorical variables were expressed as percentages and compared between groups using the χ^2 test. Characteristics at baseline were compared between individuals who developed diabetes during follow-up and those remaining free from diabetes at follow-up. Comparisons between groups were also undertaken stratified by IR (HOMA-IR ≥75th centile, HOMA ≥2.0) and overweight/obesity (BMI ≥25 kg/m^2). We used logistic regression to determine odds ratios (ORs) for developing diabetes according to the presence of *1*) a single baseline risk factor of interest, i.e., insulin resistance, overweight/obesity, fatty liver; *2*) all combinations of two of these three baseline risk factors; and *3*) all three baseline risk factors compared with the group with none of these risk factors. Analyses were repeated after adjustment for age, sex, educational status, smoking status (never, ex-, current), exercise frequency (less than once a week or at least once a week), alcohol consumption (g/day), alanine aminotransferase (ALT), and triglyceride levels. All data analysis was performed using SPSS, version 15.0 (SPSS, Chicago, IL). The statistical significance of P values in this report was set at <0.05.

RESULTS—There were 223 cases of incident diabetes during follow-up, and the characteristics of these individuals compared with the remainder of the cohort are shown in Table 1. The cohort was of working age with a preponderance of men. In the group with diabetes at follow-up, 69% of subjects had IR compared with 24% in the group remaining free from diabetes at follow-up ($P < 0.001$). In the group with diabetes at follow-up, 69% were overweight or obese and 68% had fatty liver at baseline, compared with 33% and 27%, respectively, for the group remaining free from diabetes ($P < 0.001$ for all comparisons).

Table 2 describes the characteristics of people in the following strata of BMI and insulin sensitivity

1. normal weight and insulin sensitive (Group A)
2. normal weight and insulin resistant (Group B)
3. overweight/obese and insulin sensitive (Group C)
4. overweight/obese and insulin resistant (Group D)

The prevalence of fatty liver increased incrementally across these four groups. The proportion of people with fatty liver in groups A, B, C, and D was 12, 29, 42, and 68%, respectively.

We examined the association between each of the three risk factors of interest at baseline with incident diabetes at follow-up after adjustment for age, sex, educational status, smoking, alcohol, exercise, triglyceride, and ALT. Each factor was independently associated with incident diabetes when all three were included in the model (IR: OR 3.92 [95% CI 2.86–5.37], $P < 0.0001$; overweight/obesity: 1.62 [1.17–2.24], P = 0.004; fatty liver: 2.42 [1.74–3.36], $P < 0.0001$).

Next we examined the numbers of subjects (with and without incident diabetes) who had different combinations of the risk factors of interest at baseline. There are seven potential combinations of the three risk factors of interest, and the ORs for each of these combinations are shown in Table 3 and are adjusted for *1*) age and sex; *2*) age, sex, alcohol, smoking status, and exercise and educational levels; and *3*) age, sex, alcohol, smoking status, exercise and educational levels, and triglyceride and ALT levels. Adjustment for the factors in the second model had little effect but further adjustment for triglyceride and ALT levels attenuated the

Table 1—*Baseline characteristics in individuals with and without incident diabetes at follow-up*

	No diabetes at follow-up	Diabetes at follow-up	*P*
n	12,630	223	
Age (years)	40.9 ± 6.03	42.8 ± 5.93	<0.001
Men (%)	9,013 (71)	198 (89)	<0.001
Systolic BP (mmHg)	114.6 ± 13.3	122.8 ± 15.0	<0.001
Diastolic BP (mmHg)	74.5 ± 9.9	80.2 ± 10.6	<0.001
BMI (kg/m^2)	23.8 ± 2.83	26.7 ± 3.26	<0.001
Waist circumference (cm)	82.7 ± 9.08 (*n* = 2,682)	90.1 ± 7.30 (*n* = 50)	<0.001
Glucose (mmol/L)	5.15 ± 0.46	6.05 ± 0.49	<0.001
LDL cholesterol (mmol/L)	3.07 ± 0.76	3.26 ± 0.73	<0.001
HDL cholesterol (mmol/L)	1.37 [1.21–1.58]	1.27 [1.14–1.45]	<0.001
TC (mmol/L)	5.33 ± 0.91	5.61 ± 0.93	<0.001
TG (mmol/L)	1.32 [0.94–1.89]	2.07 [1.42–2.79]	<0.001
Insulin (pmol/L)	46.3 [37.5–59.5]	63.1 [46.8–79.7]	<0.001
HOMA-IR	1.52 [1.21–1.99]	2.41 [1.83–3.02]	<0.001
Alcohol (g/day)	10.8 ± 15.1	15.6 ± 19.6	<0.001
Smoking status			
Nonsmoker	6,344 (50)	71 (32)	<0.001
Ex-smoker	2,476 (20)	52 (23)	
Current smoker	3,811 (30)	100 (45)	
Education status (years)			
≤12	3,060 (24)	62 (28)	0.017
13–14	1,111 (8.8)	27 (12)	
>14	8,460 (67)	134 (60)	
Physical activity			
None	3,601 (29)	51 (23)	0.068
<1 time/week	4,573 (36)	96 (43)	
IR	3,059 (24)	154 (69)	<0.001
Overweight/obesity	4,191 (33)	155 (69)	<0.001
Fatty liver	3,403 (27)	152 (68)	<0.001

Data are mean ± SD, median [interquartile range] for continuous variables, or *n* (%) for categorical variables. BP, blood pressure; TC, total cholesterol; TG, triglyceride.

ORs slightly. Of the 223 incident cases of diabetes identified at follow-up, 26 people had none of the risk factors of interest, 37 had one, 56 had two, and 104 had three risk factors at baseline. In the fully adjusted model, the OR (95% CIs) for incident diabetes for the presence of all three risk factors at baseline was 14.13 (8.99–22.21). The data in Table 3 also describe how the three factors of interest cluster together. Among people with one or more risk factors of interest in the whole cohort, the largest proportion (34%) had overweight/obesity alone compared with 28% with fatty liver and 25% with IR as single risk factors. The least frequent combination of two risk factors, occurring among 3% of people, was the combination of IR and fatty liver in the absence of overweight/obesity. All three factors occurred together in 10% of people in the whole cohort at baseline. In contrast, in the group with incident diabetes, the cluster of all three risk factors together occurred in 104/223 (47%) of subjects, whereas only 26/223 (12%) had none of these risk factors of interest.

CONCLUSIONS—We have quantified for the first time the powerful impact of the combined presence of IR, overweight/obesity, and fatty liver on the odds of developing diabetes. Importantly, we have established that each of these factors is independently associated with incident diabetes after adjustment for the other two risk factors and other relevant factors. Almost half of the subjects with incident type 2 diabetes at 5-year follow-up had all three risk factors at baseline, but this cluster occurred in only approximately 10% of the population that did not develop diabetes. Only 12% of incident cases of diabetes at follow-up did not have any of these three risk factors at baseline compared with ~47% in the general population. Thus, the presence of all three risk factors occurring together was common in subjects who develop diabetes, emphasizing the importance and the frequency of the clustering of these three risk factors for type 2 diabetes.

We have shown previously that fatty liver is a predictor of diabetes, independently of IR (11), and others have shown that fatty liver is a risk factor for incident diabetes (21–23). In a study of Japanese men of similar age to the participants in our study, Shibata et al. (21) showed that fatty liver at baseline was associated with an age and BMI adjusted hazard ratio of 5.5 (95% CI [3.6–8.5], $P < 0.001$) for incident diabetes at 4-year follow-up. Our results extend the work of these authors as we show that there is also an additional strong association between fatty liver and incident diabetes, independently of IR, and we have quantified the risk of having all three risk factors.

A diagnosis of fatty liver can be established noninvasively using techniques such as magnetic resonance spectroscopy, computed tomography, or ultrasound but, recently, proxy markers for nonalcoholic fatty liver disease (e.g., the nonalcoholic fatty liver disease–fatty liver score and the fatty liver index that are generated from anthropometric and biochemical measurements) have also been found to be associated with incident diabetes independently of potential confounding factors (24).

Of the three risk factors of interest, overweight/obesity had the weakest association with incident diabetes (fully adjusted OR for overweight/obesity alone: 1.29 [0.62–2.71]) and IR had strongest association (fully adjusted OR for IR alone: 3.66 [1.89–7.08]). BMI provides a general measure of obesity and does not reflect regional fat distribution. It is possible that measures of central obesity such as waist circumference would have a stronger relationship with diabetes than BMI, but unfortunately waist measurements were not available for all cohort participants. The OR for incident diabetes was highest for the combination of IR, overweight/obesity, and fatty liver (fully adjusted OR 14.13 [8.99–22.2]). Tests for interaction (data not shown but available from authors) showed no statistically significant superadditive or synergistic association of the three factors with incident diabetes, but this may reflect the limited power of the study to detect statistically significant interactions.

Although the most frequent combination of risk factors among subjects that

Table 2—*Baseline characteristics stratified by overweight/obesity and IR*

HOMA centile, <75th centile, or ≥75th centile	Normal weight			Overweight/Obese		
	Group A	Group B		Group C	Group D	
	Not insulin resistant	Insulin resistant	*P*	Not insulin resistant	Insulin resistant	*P*
N	7,174	1,333		2,466	1,880	
Age (years)	40.6 ± 5.99	40.5 ± 6.26	0.48	41.7 ± 5.91	41.6 ± 6.05	0.62
SBP (mmHg)	112.1 ± 12.4	114.4 ± 13.5	<0.001	118.0 ± 13.0	120.9 ± 14.4	<0.001
DBP (mmHg)	72.7 ± 9.3	73.9 ± 9.7	<0.001	77.4 ± 9.8	79.0 ± 10.4	<0.001
Glucose (mmol/L)	5.05 ± 0.44	5.38 ± 0.46	<0.001	5.18 ± 0.45	5.46 ± 0.49	<0.001
LDL (mmol/L)	2.95 ± 0.74	3.04 ± 0.76	<0.001	3.25 ± 0.75	3.31 ± 0.77	0.007
HDL (mmol/L)	1.42 [1.24–1.6]	1.38 [1.19–1.58]	<0.001	1.32 [1.18–1.50]	1.28 [1.14–1.43]	<0.001
TC (mmol/L)	5.18 ± 0.88	5.34 ± 0.94	<0.001	5.55 ± 0.90	5.63 ± 0.91	0.003
TG (mmol/L)	1.13 [0.84–1.6]	1.39 [0.97–2.04]	<0.001	1.58 [1.14–2.19]	1.93 [1.41–2.63]	<0.001
Insulin (pmol/L)	40.6 [34.4–47.9]	67.6 [62.9–75.4]	<0.001	45.1 [38.7–51.8]	71.5 [64.7–82.7]	<0.001
HOMA-IR	1.32 [1.10–1.50]	2.30 [2.13–2.59]	<0.001	1.50 [1.28–1.75]	2.47 [2.20–2.87]	<0.001
BMI (kg/m^2)	22.2 ± 1.86	22.9 ± 1.67	<0.001	26.6 ± 1.39	27.4 ± 1.95	<0.001
Fatty liver	850 (12)	388 (29)	<0.001	1,032 (42)	1,285 (68)	<0.001

Data are mean ± SD, median [interquartile range] for continuous variables, or *n* (%) for categorical variables. DBP, diastolic blood pressure; HDL, HDL cholesterol; LDL, LDL cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

developed diabetes was the presence of all three factors, 56/223 (25%) had only two of the three risk factors. Of the different possible combinations of two risk factors, the data suggested that the combination of overweight/obesity and fatty liver (in the absence of IR) was associated with the lowest odds of diabetes (OR 3.23 [95% CI 1.78–5.89]) and the combination of IR and fatty liver had the strongest association with diabetes (6.73 [3.49–12.73]), although CIs are wide and overlap for these estimates. Fatty liver is emerging as an independent risk factor for diabetes, and our data suggest that its association with incident diabetes may be stronger than that of overweight/obesity and weaker than that of IR. However, regardless of the relative strengths of these risk factors for diabetes, there was a striking and marked increase in odds of diabetes with the occurrence of all three risk factors. The fact that they all have independent effects of each other suggests that targeted specific approaches to ameliorating the effects of each individual risk factor may have a considerable impact on decreasing risk of diabetes.

In support of the notion that IR, obesity, and fatty liver each act via different mechanisms to increase risk of diabetes, it has been shown recently that combined metformin and rosiglitazone treatment has discordant effects on central obesity, hepatic IR, and fatty liver (25). These investigators showed that although the rosiglitazone and metformin combination had no effect on central obesity, the combination has a transient effect on hepatic insulin sensitivity and a sustained effect on ALT (as a proxy marker for fatty liver). Overweight/obesity may increase fat accumulation in key insulin-sensitive tissues such as liver (26) and when fat accumulation occurs in liver, hepatic IR occurs via mechanisms that increase gluconeogenesis, decrease glycogen synthesis, and inhibit insulin signaling (15,16). Physical inactivity is associated with hepatic IR (27) and modest increases in physical activity have recently been shown to be very effective in improving liver enzymes (28) and decreasing liver fat (29–33). It is likely that

Table 3—*OR for incident diabetes at follow-up for different combinations of IR, overweight/obesity, and fatty liver*

	n/proportions with incident diabetes (%)	OR [95% CI] *P*		
		Model 1	Model 2	Model 3
Whole cohort	223/12,853 (1.7)			
No risk factors	26/6,324 (0.4)	1	1	1
IR alone	14/945 (1.5)	3.95 [2.05–7.61] <0.001	4.06 [2.10–7.82] <0.001	3.66 [1.89–7.08] <0.001
Overweight/obesity alone	10/1,434 (0.7)	1.46 [0.70–3.05] 0.310	1.39 [0.67–2.90] 0.382	1.29 [0.62–2.71] 0.50
Fatty liver alone	13/850 (1.5)	3.28 [1.67–6.44] <0.001	3.36 [1.71–6.60] <0.001	2.73 [1.38–5.41] 0.004
IR and overweight/obesity	21/595 (3.5)	7.78 [4.33–13.96] <0.001	7.51 [4.18–13.50] <0.001	6.16 [3.38–11.22] <0.001
IR and fatty liver	15/388 (3.9)	8.42 [4.40–16.09] <0.001	8.73 [4.56–16.71] <0.001	6.73 [3.49–12.97] <0.001
Overweight/obesity and fatty liver	20/1,032 (1.9)	4.07 [2.25–7.38] <0.001	4.03 [2.22–7.30] <0.001	3.23 [1.78–5.89] <0.001
IR, overweight/obesity, and fatty liver	104/1,285 (8.1)	18.27 [11.72–28.46] <0.001	18.27 [12.00–29.21] <0.001	14.13 [8.99–22.2] <0.001

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, alcohol, smoking status, exercise, and educational status. Model 3 adjusted for age, sex, alcohol, smoking status, exercise, educational status, triglyceride, and ALT.

relatively small increases in physical activity levels may decrease risk of type 2 diabetes in middle-aged individuals, not only through accepted improvements in improved glucose utilization and the promotion of weight loss, but also via a beneficial impact on liver fat and hepatic insulin sensitivity. Thus, the marked benefit on diabetes risk of increases in physical activity may be acting favorably to modify each of the three major risk factors that we have investigated in the current study.

Our study has some limitations. We have used routine clinical data from an occupational cohort with a preponderance of men. Although ultrasonography is a reasonably accurate technique for detecting modest amounts of liver fat (>30% liver fat infiltration), ultrasound has limited sensitivity to detect minor amounts of fatty infiltration. Oral glucose tolerance tests were not performed so subjects with isolated 2-h postchallenge hyperglycemia at follow-up have been identified. Data were not available on family history of diabetes, participants' lifetime exposure to alcohol, or use of drugs known to be associated with increased risk of diabetes (although heavy alcohol consumption and use of drugs of interest is likely to be present only in a small percentage of people in this middle-aged occupational cohort). Data on waist circumference and inflammatory markers were incomplete (only available on approximately 18% of the cohort), and therefore we were unable to use these data. Additionally, we only had basic self-reported information on physical activity levels in this cohort, and consequently it is likely that estimates are highly likely to be subject to measurement error. The study is limited to one ethnic group, and the distribution of risk factors and their association with diabetes may differ by ethnic group. Our study was not large enough to investigate whether the identification of fatty liver provides a valuable addition to diabetes risk scores to improve risk prediction of diabetes, and further research in several populations is required to address this important issue.

In conclusion, in a middle-aged occupational cohort study, we have shown that IR, overweight/obesity, and fatty liver commonly occur together and that each is independently associated with increased odds of developing type 2 diabetes. We have quantified the cumulative impact of different combinations of IR, overweight/obesity, and fatty liver, and shown that the occurrence of all three risk factors together markedly increases the risk of developing diabetes. Further research is needed to understand the separate pathogenetic mechanisms by which IR, overweight/obesity, and fatty liver contribute individually to the development of type 2 diabetes. It is also necessary to identify whether effectiveness of lifestyle and pharmaceutical interventions vary for people with different combinations of risk factors.

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K.-C.S. devised the hypothesis, analyzed data, and wrote the RESEARCH DESIGN AND METHODS and CONCLUSIONS sections. W.-S.J. reviewed the manuscript and contributed to discussion. S.H.W. reviewed and edited the manuscript and contributed to discussion. C.D.B. devised the hypothesis and wrote the introduction and CONCLUSIONS sections. K.-C.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Leahy JL. Pathogenesis of type 2 diabetes mellitus. Arch Med Res 2005;36:197–209
2. Karaca M, Magnan C, Kargar C. Functional pancreatic beta-cell mass: involvement in type 2 diabetes and therapeutic intervention. Diabetes Metab 2009;35:77–84
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
4. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444:840–846
5. Eckel RH, Kahn SE, Ferrannini E, et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? J Clin Endocrinol Metab 2011;96:1654–1663
6. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005;365:1333–1346
7. Ferrannini E, Gastaldelli A, Iozzo P. Pathophysiology of prediabetes. Med Clin North Am 2011;95:327–339, vii–viii
8. Kotronen A, Seppälä-Lindroos A, Bergholm R, Yki-Järvinen H. Tissue specificity of insulin resistance in humans: fat in the liver rather than muscle is associated with features of the metabolic syndrome. Diabetologia 2008;51:130–138
9. Holt HB, Wild SH, Wood PJ, et al. Nonesterified fatty acid concentrations are independently associated with hepatic steatosis in obese subjects. Diabetologia 2006;49:141–148
10. Yamada T, Fukatsu M, Suzuki S, Wada T, Yoshida T, Joh T. Fatty liver predicts impaired fasting glucose and type 2 diabetes mellitus in Japanese undergoing a health checkup. J Gastroenterol Hepatol 2010;25:352–356
11. Sung KC, Kim SH. Interrelationship between fatty liver and insulin resistance in the development of type 2 diabetes. J Clin Endocrinol Metab 2011;96:1093–1097
12. Kim CH, Park JY, Lee KU, Kim JH, Kim HK. Fatty liver is an independent risk factor for the development of type 2 diabetes in Korean adults. Diabet Med 2008;25:476–481
13. Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. Effects of nonalcoholic fatty liver disease on the development of metabolic disorders. J Gastroenterol Hepatol 2007;22:1086–1091
14. Kantartzis K, Machann J, Schick F, Fritsche A, Häring HU, Stefan N. The impact of liver fat vs visceral fat in determining categories of prediabetes. Diabetologia 2010;53:882–889
15. Gao Z, Zhang J, Kheterpal I, Kennedy N, Davis RJ, Ye J. Sirtuin 1 (SIRT1) protein degradation in response to persistent c-Jun N-terminal kinase 1 (JNK1) activation contributes to hepatic steatosis in obesity. J Biol Chem 2011;286:22227–22234
16. Samuel VT, Liu ZX, Qu X, et al. Mechanism of hepatic insulin resistance in nonalcoholic fatty liver disease. J Biol Chem 2004;279:32345–32353
17. Amaro A, Fabbrini E, Kars M, et al. Dissociation between intrahepatic triglyceride content and insulin resistance in familial hypobetalipoproteinemia. Gastroenterology 2010;139:149–153
18. Lockman KA, Nyirenda MJ. Interrelationships between hepatic fat and insulin resistance in non-alcoholic fatty liver disease. Curr Diabetes Rev 2010;6:341–347
19. Stefan N, Staiger H, Häring HU. Dissociation between fatty liver and insulin resistance: the role of adipose triacylglycerol lipase. Diabetologia 2011;54:7–9
20. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. Br Med J (Clin Res Ed) 1986;292:13–15
21. Shibata M, Kihara Y, Taguchi M, Tashiro M, Otsuki M. Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. Diabetes Care 2007;30:2940–2944

22. Friis-Liby I, Aldenborg F, Jerlstad P, Rundström K, Björnsson E. High prevalence of metabolic complications in patients with non-alcoholic fatty liver disease. Scand J Gastroenterol 2004;39:864–869
23. Ekstedt M, Franzén LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865–873
24. Balkau B, Lange C, Vol S, Fumeron F, Bonnet F; Group Study D.E.S.I.R. Nine-year incident diabetes is predicted by fatty liver indices: the French D.E.S.I.R. study. BMC Gastroenterol 2010;10:56
25. Retnakaran R, Ye C, Hanley AJ, Harris SB, Zinman B. Discordant effects on central obesity, hepatic insulin resistance, and alanine aminotransferase of low-dose metformin and thiazolidinedione combination therapy in patients with impaired glucose tolerance. Diabetes Obes Metab 2012;14:91–93
26. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–887
27. Holt HB, Wild SH, Wareham N, et al. Differential effects of fatness, fitness and physical activity energy expenditure on whole-body, liver and fat insulin sensitivity. Diabetologia 2007;50:1698–1706
28. St George A, Bauman A, Johnston A, Farrell G, Chey T, George J. Independent effects of physical activity in patients with nonalcoholic fatty liver disease. Hepatology 2009;50:68–76
29. Byrne CD, Olufadi R, Bruce KD, Cagampang FR, Ahmed MH. Metabolic disturbances in non-alcoholic fatty liver disease. Clin Sci (Lond) 2009;116:539–564
30. Finucane FM, Sharp SJ, Purslow LR, et al. The effects of aerobic exercise on metabolic risk, insulin sensitivity and intrahepatic lipid in healthy older people from the Hertfordshire Cohort Study: a randomised controlled trial. Diabetologia 2010;53:624–631
31. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121–129
32. Kantartzis K, Thamer C, Peter A, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. Gut 2009;58:1281–1288
33. Hallsworth K, Fattakhova G, Hollingsworth KG, et al. Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut 2011;60:1278–1283