Diagnosis accuracy of ALT and waist circumference as a screening test for insulin resistance

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Abstract

ALT and waist circumference are both correlated to insulin resistance (IR).

Objective : **To determine whether ALT provides information in addition to waist circumference for identifying IR.**

Methods : **IR was defined by HOMA-IR index ≥3. In this Europid population, a waist circumference ≥80 cm in women and ≥94 cm in men was considered excessive. Elevated ALT was defined using either the usual cut-off or updated cut-offs of 19 U/l in women and 30 U/l in men.**

Results : **288 participants without medication affecting insulin concentration were included. 81 (28%) were insulin resistant, 30 (10%) and 98 (34%) had increased ALT using usual and updated cut-offs, respectively, and 218 (76%) had excessive waist circumference. Among subjects with normal waist circumference, IR was as frequent in participants with normal ALT as in those with increased ALT. Among subjects with excessive waist circumference, IR was less frequent in participants with normal ALT according to the usual cut-off (31% vs. 56%, p=0.01), and tended to be less frequent in participants with normal ALT according to updated cut-offs (29% vs. 41%, p=0.07) than in those with increased ALT.**

Conclusion : **ALT is useful for identifying IR only if waist circumference is excessive. In subjects with excessive waist circumference, IR is present in more than 40% in women with ALT >19 U/l and in men with ALT >30 U/l, and in more than 50% in individuals with ALT >45 U/l.** (Acta gastroenterol. belg., **2016**, 79, **455-462**).

Key words : alanine aminotransferase, homeostasis model assessment of insulin resistance, non-alcoholic fatty liver disease; metabolic diseases.

Abbreviations : ALT, alanine aminotransferase ; BMI, body mass index ; CI, confidence interval ; HCC, hepatocellular carcinoma ; HOMA-IR, homeostasis model assessment of insulin resistance ; NAFLD, non-alcoholic fatty liver disease.

Introduction

Insulin resistance is a major public health problem. Insulin resistance is associated with type 2 diabetes mellitus and the metabolic syndrome, as well as increased cardiovascular morbidity. In patients with non-alcoholic fatty liver disease (NAFLD), insulin resistance leads to hepatic accumulation of diacylglycerol which decreases insulin signaling in the liver (1,2). In addition, diabetes and insulin resistance are risk factors for progressive liver fibrosis in many liver diseases and are associated with the development of hepatocellular carcinoma (3-6), the incidence of which has greatly increased during the last years (7,8). Insulin resistance may also influence treatment efficacy in several liver diseases (9). Finally, in some instances, insulin resistance is a therapeutic target for patients with chronic liver disease such as NAFLD patients in whom different therapeutic strategies have been designed to improve insulin sensitivity (10).

The homeostasis model assessment of insulin resistance (HOMA-IR) index is a simplification of a mathematical model in which fasting glucose and insulin values are plotted to allow assessment of insulin sensitivity (11). In epidemiological studies, the HOMA-IR index offers an easy-to-use tool for determining differences in insulin sensitivity status between groups; in the clinical setting, it is a robust surrogate method to estimate insulin resistance (11). The HOMA-IR index has demonstrated good correlations with the hyperinsulinemic-euglycemic glucose clamp, the gold standard for measuring insulin sensitivity (12). Although cut-off values for defining insulin resistance differ according to the ethnicity and the metabolic condition of the population studied, values around 3 have been proposed to define insulin resistance in healthy European subjects (13-15).

Alanine aminotransferase (ALT) is the most commonly used laboratory test for detecting liver disease. It is independently related to body mass index (BMI) and to other features of metabolic syndrome, and is commonly used as a surrogate marker of NAFLD in patients with no other cause of liver disease (16). Many studies have demonstrated that ALT is correlated to liver triglyceride content and to insulin resistance assessed by different means including the HOMA-IR index (17-22). In clinical trials designed to improve insulin sensitivity in NAFLD, ALT is often used as a surrogate marker of improved outcome (10). However, the correlation between ALT and insulin resistance is imperfect and ALT often fails to identify patients with minimal to mild necro-inflammatory activity (23,24). As the range of ALT

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currently defined as "normal" may underestimate the prevalence of liver disease, Prati *et al*., in 2002, proposed redefining the normal range of ALT according to sex (25). Cut-offs of 19 U/l in women and 30 U/l in men had the highest predictive value in identifying liver diseases such as NAFLD; thus, these lower cut-offs could better define the true normal range of ALT and might be more appropriate to identify insulin resistance.

Waist circumference is strongly linked to insulin resistance (26,27). According to the definition of the International Diabetes Federation, waist circumferences ^{3}80 cm in women and ^{3}94 cm in men (which define central obesity) are the only mandatory criteria for establishing a diagnosis of metabolic syndrome in Europeans (10). Measurement of waist circumference has been proposed as a guide to determine insulin sensitivity (10). To date, no study has combined the use of waist circumference and ALT in screening for insulin resistance. In the present study, carried out in a general population of individuals with no medication affecting insulin concentration, we sought to assess the usefulness of waist circumference and ALT in screening for insulin resistance assessed by the HOMA-IR index.

Materials and methods

Participants

Participants were between 20 and 80 years of age and were recruited from pre-operative consultations prior to minor surgery (in the field of ophthalmology, otorhinolaryngology, orthopedics, gynecology or digestive surgery) scheduled at a one-day clinic. For each participant, weight, height, waist circumference and blood pressure were measured. Participants were asked about their medical history and treatments for diabetes mellitus, hypertension and dyslipidemia. Data on alcohol consumption were obtained from a questionnaire that included items about the type of alcoholic beverages consumed, the frequency of alcohol consumption on a weekly basis and the usual amount consumed each time. The daily amount of pure alcohol intake (g/day) was calculated using this data. We excluded patients with a history of, or who were treated for diabetes, to avoid the potential confounding effect of treatments. Participants with excessive (> 30 g/day) alcohol intake were not excluded from the study. The study was approved by the Ethical Committee of Jolimont Hospital (Ref. 2008/10). All patients gave written informed consent.

Blood analysis

Blood analyses were performed after overnight fasting in the same laboratory using identical techniques in all patients. Serum levels of ALT, aspartate aminotransferase, bilirubin, γ-glutamyl transpeptidase, glucose, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were analyzed. Serum levels of ALT were assessed according to the International Federation of Clinical Chemistry using the Roche/Hitachi cobas c systems. In our laboratory, the upper limit of normal range for ALT was 45 U/l. The serum insulin concentration was measured by the electrochemiluminescent immunoassay method on Elecsys and cobas e analyzers.

Definitions

Normal ALT values were defined according either to the upper limit of normal range (45 U/l) or to Prati's article with the lower cut-offs at ≤19 U/l in women and ≤30 U/l in men(25). The latter are referred as "updated cut-offs". The presence of metabolic syndrome and waist circumference were assessed according to the definition of the International Diabetes Federation (28). In this European population, central obesity was defined as a waist circumference ≥80 cm in women or ≥94 cm in men.

Endpoints

Insulin resistance was estimated using the HOMA-IR index, which was calculated using the following formula: HOMA-IR index = (insulin (mU/ml) x (fasting glucose (mmol/l)/22.5)). Insulin resistance was defined by a HOMA-IR index of at least 3, which was close to the 75th percentile in the population studied (see Results, factors associated with insulin resistance). Since the cut-off for HOMA-IR in identifying IR is not clear-cut, sensitivity analysis was also performed, taking into account a cut-off of 2.5.

Statistical analysis

Data were expressed as percentage or median (95% CI). In a first step, parameters associated with insulin resistance, increased ALT and excessive waist circumference were assessed. In a second step, we assessed the diagnostic accuracy of waist circumference and ALT as screening tools for insulin resistance. Analyses were conducted using variance analysis, the chi-square test, two-sided Fisher exact test, Mann-Whitney test, Wilcoxon test and two-sample Student's t-test when appropriate. All statistical testing was two-tailed at the 5% level.

All statistical analyses were performed using NCSS 2007 software (NCSS, Kaysville, UT, USA).

Results

Study population

Among the 337 participants who attended a pre-operative consultation prior to minor surgery between January 2009 and February 2011, 49 were excluded for the following reasons: 38 because they had a history of diabetes and/or were treated with antidiabetic medication, 10 because HOMA-IR was not available and 1 because waist circumference was not determined. Thus, 288 participants were included. Pertinent characteristics of participants are shown in Table 1. As daily intake of

small amounts of alcohol could be considered beneficial, baseline characteristics were also assessed according to alcohol intake (Table 2).

Factors associated with insulin resistance

Median HOMA-IR index was 1.9 (25th percentile: 1.1, 75th percentile: 3.1, extremes: 0.04 – 51.3). Eighty-one subjects (28%) were insulin resistant. Pertinent characteristics of participants with or without insulin resistance are shown in Table 1.

Factors associated with increased ALT and with excessive waist circumference

Thirty subjects (10%) had increased ALT using usual cut-offs and 98 (34%) had increased ALT using updated cut-offs; 218 (76%) had excessive waist circumference. The characteristics of participants with normal or increased ALT according to usual and updated cut-offs and the characteristics of participants with normal or excessive waist circumferences are shown in Table 3.

Usefulness of ALT and waist circumference in screening for insulin resistance

In a first step, we assessed the diagnostic accuracy of ALT and of waist circumference in screening for insulin resistance (Table 3). The usual ALT cut-off identified 14 of the 81 (17%) insulin resistant subjects. Subjects with normal ALT according to the usual cut-off had lower HOMA-IR indexes (1.7 vs. 2.9, p=0.004) and were less frequently insulin resistant (26% vs. 47%, p=0.02) than those with elevated ALT. Updated ALT cut-offs identified 35 (43%) insulin resistant subjects. Subjects with normal ALT according to updated cut-offs had lower HOMA-IR indexes (1.6 vs. 2.2, p=0.001) and were less frequently insulin resistant (24% vs. 36%, p=0.04) than those with elevated ALT. Excessive waist circumference identified 73 (90%) insulin resistant subjects. Subjects with normal waist circumference had lower HOMA-IR indexes (1.2 vs. 2.2, p<0.001) and were less frequently insulin resistant (11% vs. 33%, p<0.001) than those with excessive waist circumference. Table 4 provides the sensitivity, specificity and the related positive and negative predictive values of

Table 1. — **Baseline demographic and clinical characteristics of the study population**

Characteristics	Whole study group (n=288)	Participants without IR (n=207)	Participants with IR (n=81)	*p-Value*
Age (years) *	55 (52-57)	52 (49-56)	60 (56-62)	0.002
Sex ratio (no. of males, %)	133 (46%)	99 (48%)	34 (42%)	0.4
Ethnicity (n Caucasians, %) **	191 (99%)	131 (100%)	60 (98%)	0.8
BMI (kg/m^2) *	27.3 (26.7-27.8)	26.1 (25.4-26.9)	29.8 (29.3-31.8)	<0.0001
Waist circumference (cm) *	95 (93-97)	92 (90-94)	102 (99-105)	<0.0001
Systolic blood pressure (mmHg) *	120 (120-125)	120 (120-120)	125 (120-130)	0.01
Diastolic blood pressure (mmHg) *	60 (60-60)	60 (60-60)	60 (60-70)	0.04
AST (U/l) *	21 (20-22)	21 (20-22)	22 (21-25)	0.1
ALT (U/l) *	19 (17-21)	18 (17-20)	22 (19-26)	0.007
GGT (U/l) *	24 (21-26)	21 (19-25)	28 (25-32)	0.02
Glucose (mg/dl) *	92 (89-94)	88 (86-90)	107 (101-117)	<0.0001
Insulin (mU/l) *	8.4 (7.4-9.0)	6.3 (5.7-7.1)	17.5 (15.7 -19.4)	<0.0001
HOMA-IR index *	1.9 (1.6-2.1)	1.4 (1.3-1.5)	4.9 (3.9-5.5)	<0.0001
Total cholesterol (mg/dl) *	191 (184-198)	194 (184-199)	185 (173-197)	0.2
HDL-C (mg/dl) *	53 (50-54)	54 (52-56)	48 (45-51)	0.003
LDL-C (mg/dl) *	110 (104-116)	111 (104-122)	106 (98-119)	0.4
TG (mg/dl) *	103 (95-109)	98 (88-106)	124 (103-139)	0.003
Metabolic syndrome (no. of positives, %) ***	124 (44%)	63 (31%)	61 (77%)	<0.0001
Alcohol consumption (no. of consumers, %) ****	114 (57%)	81 (59%)	33 (54%)	0.5
Alcohol consumption (g/day) * ****	7 (3-10)	7 (3-11)	8 (3-13)	0.7

* Data expressed as median (95% CI); ** assessed in 192 patients; *** assessed in 284 patients; **** assessed in 199 patients
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GGT, g-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides

Table 2. — **Characteristics of the study population according to alcohol intake**

Characteristics	Participants without alcohol intake (n=85)	Participants with moderate alcohol intake (≤ 30 g/day) (n=104)	Participants with excessive alcohol intake (> 30 g/day) (n=10)	*p-Value*
Age (years) *	53 (48-59)	56 (52-59)	53 (40-64)	0.6
Sex ratio (no. of males, %)	133 (46%)	99 (48%)	34 (42%)	0.4
Ethnicity (n Caucasians, %) **	82 (99%)	101 (100%)	8 (100%)	0.5
BMI (kg/m^2) *	27.5 (25.5-29.2)	27.3 (26.1-28.2)	25.6 (20.6-28.9)	0.3
Waist circumference (cm) *	93 (87-97)	95 (90-97)	94 (82-108)	0.6
Systolic blood pressure (mmHg) *	120 (120-120)	120 (120-125)	125 (120-150)	0.2
Diastolic blood pressure (mmHg) *	60 (60-60)	60 (60-70)	65 (60-80)	0.6
AST (U/l) *	20 (19-21)	22 (20-24)	21 (16-49)	0.3
ALT (U/l) *	17 (15-20)	19 (17-22)	19 (11-32)	0.11
GGT (U/l) *	18 (16-22)	24 (20-28)	44 (22-296)	0.002
Glucose (mg/dl) *	89 (86-93)	92 (88-95)	93 (72-100)	0.7
Insulin (mU/l) *	8.9 (7.5-11.1)	7.6 (6.3-9.0)	6.7 (1.6 -14.3)	0.18
HOMA-IR index *	2.1 (1.5-2.6)	1.7 (1.4-2.2)	1.4 (0.3-3.4)	0.3
HOMA-IR index >3 (no., %)	28 (33%)	31 (30%)	2 (20%)	0.7
Total cholesterol (mg/dl) *	189 (176-198)	197 (183-210)	231 (144-263)	0.2
HDL-C (mg/dl) *	52 (48-57)	53 (50-56)	45 (36-69)	0.3
LDL-C (mg/dl) *	111 (102-119)	112 (103-126)	126 (52-164)	0.7
TG (mg/dl) *	95 (85-110)	98 (85-108)	152 (117-443)	0.008
Metabolic syndrome (no. of positives, %) ***	35 (42%)	41 (40%)	4 (40%)	1.0
Alcohol consumption (no. of consumers, %) ****	0 (0%)	104 (100%)	10 (100%)	<0.001
Alcohol consumption (g/day) * ****	0	5 (3-9)	43 (35-66)	<0.001

* Data expressed as median (95% CI); ** assessed in 192 patients; *** assessed in 197 patients; **** assessed in 199 patients
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GGT, g-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides

usual and updated ALT cut-offs for screening for insulin resistance in the whole study group and in patients with increased and normal waist circumference.

In a second step, we analyzed the extent to which ALT could provide information in addition to waist circumference for identification of insulin resistance. Thus, we separated participants into 4 groups: normal waist circumference and normal ALT; normal waist circumference and increased ALT; excessive waist circumference and normal ALT; and excessive waist circumference and increased ALT. We then assessed the prevalence of insulin resistance in the 4 groups using both the usual ALT cut-off (Table 5) and updated ALT cut-offs (Table 6).

Among the 70 participants with normal waist circumference, 8 (11%) were insulin resistant. The prevalence of insulin resistance was similar among participants with normal and with increased ALT, whatever the ALT cut-off used (Tables 5 and 6). Considering a lower HOMA-IR cut-off of 2.5 for defining insulin resistance did not modify the results (Tables 5 and 6).

Among the 218 participants with excessive waist circumference, 73 (33%) were insulin resistant. Increased ALT according to the usual cut-off identified 13 of these 73 insulin resistant subjects (18%). The prevalence of insulin resistance was significantly lower in participants with normal ALT according to the usual cut-off than in those with increased ALT (31% vs. 56%, p=0.001) (Table 4). Increased ALT according to updated ALT cut-offs identified 34 of the 73 insulin resistant subjects (47%). The prevalence of insulin resistance was numerically lower in participants with normal ALT according to updated cut-offs than in those with increased ALT (29% vs. 41%, p=0.07) (Table 5). The predictive value of ALT in participants with excessive waist circumference was confirmed by higher median ALT in those who were insulin resistant compared to those who were not (24 vs. 20 IU/ml, p=0.03). Considering a lower cut-off of 2.5

Table 3. — **Characteristics of the study population according to ALT and waist circumference**

Characteristics	**Normal ALT (n=258)**	**Increased ALT (n=30)**	***p-Value***	**Normal updated ALT (n=190)**	**Increased updated ALT (n=98)**	***p-Value***	**Normal waist circumference (n=70)**	**Excessive waist circumference (n=218)**	***p-Value***
Age (years) *	56 (53-58)	44 (40-57)	0.01	55 (52-58)	55 (49-59)	0.5	49 (44-54)	57 (54-59)	0.006
Sex ratio (no. of males, %)	113 (44%)	20 (67%)	0.02	93 (49%)	40 (41%)	0.2	40 (57%)	93 (43%)	0.03
Ethnicity (n Caucasians, %) **									
BMI (kg/m^2) *	27.1 (26.5-27.7)	29.2 (26.1-32.7)	0.04	26.8 (25.7-27.4)	28.5 (27.4-29.8)	<0.001	22.8 (22.0-24.0)	28.5 (28.0-29.4)	<0.001
Waist circumference (cm) *	95 (92-96)	97 (94-104)	0.05	93 (90-95)	98 (95-100)	0.002	80 (78-84)	98 (97-100)	<0.001
Systolic blood pressure (mmHg) *	120 (120-120)	130 (120-130)	0.03	120 (120-120)	125 (120-130)	0.05	120 (115-120)	120 (120-125)	0.003
Diastolic blood pressure (mmHg) *	60 (60-60)	70 (60-80)	0.06	60 (60-60)	60 (60-70)	0.1	60 (60-60)	60 (60-60)	0.01
AST (U/l) *	20 (20-21)	37 (33-52)	<0.001	19 (17-20)	29 (27-33)	<0.001	20 (17-21)	22 (20-23)	0.054
ALT (U/l) *	18 (17-19)	59 (53-68)	<0.001	15 (15-17)	36 (31-39)	<0.001	16 (14-17)	21 (19-22)	<0.001
GGT (U/l) *	22 (19-24)	62 (42-79)	<0.001	19 (17-21)	36 (30-45)	<0.001	17 (15-20)	26 (23-29)	0.002
Glucose (mg/dl) *	91 (89-94)	94 (89-98)	0.4	91 (88-94)	92 (89-96)	0.3	86 (80-89)	93 (91-96)	0.001
Insulin (mU/l) *	7.8 (7.1-8.8)	11.3 (8.9-15.2)	0.003	7.3 (6.3-8.5)	9.8 (8.5-11.4)	<0.001	5.8 (4.5-7.1)	9.5 (8.5-10.3)	<0.001
HOMA-IR *	1.7 (1.5-2.0)	2.9 (2.1-3.8)	0.004	1.6 (1.5-1.9)	2.2 (1.9-2.7)	0.001	1.2 (0.9-1.6)	2.2 (1.9-2.4)	<0.001
HOMA-IR > 2.5 (no. of positives, %)	84 (33%)	16 (53%)	0.02	58 (30%)	42 (43%)	0.04	9 (13%)	91 (42%)	<0.001
HOMA-IR > 3 (no. of positives, %)	67 (26%)	14 (47%)	0.02	46 (24%)	35 (36%)	0.04	8 (11%)	73 (33%)	<0.001
Total cholesterol (mg/dl) *	189 (182-198)	204 (185-229)	0.02	189 (181-198)	194 (184-205)	0.2	194 (180-205)	190 (184-198)	0.6
HDL cholesterol (mg/dl) *	53 (50-55)	51 (44-57)	0.7	53 (50-56)	52 (48-55)	0.6	59 (54-64)	50 (49-53)	<0.001
LDL cholesterol (mg/dl) *	107 (102-114)	126 (109-137)	0.07	107 (101-114)	115 (106-126)	0.2	111 (102-123)	109 (102-115)	0.8
Triglycerides (mg/dl) *	98 (91-107)	138 (117-189)	<0.001	95 (88-106)	111 (101-126)	0.04	86 (72-98)	107 (102-117)	<0.001
Metabolic syndrome (no. of positives, %) ***	107 (42%)	17 (57%)	0.1	68 (36%)	56 (58%)	<0.001	0 (0%)	124 (58%)	<0.001
Alcohol consumption (no. of consumers, %) ****	100 (56%)	14 (67%)	0.4	74 (56%)	40 (60%)	0.6	29 (59%)	85 (57%)	0.8
Alcohol consumption (g/day) * ****	8 (3-11)	3 (2-13)	0.7	8 (3-11)	4 (2-11)	0.7	5 (3-11)	8 (3-11)	0.8

* Data expressed as median (95% CI); ** assessed in 192 patients; *** ** assessed in 284 patients; **** assessed in 199 patients

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, g-glutamyl transpeptidase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein

HOMA-IR index for defining insulin resistance did not modify the results (Tables 5 and 6).

Discussion

Although increased waist circumference and increased BMI are well known cardiovascular risk factors, cardiovascular risk profile is currently not assessed in all patients at risk. In addition, measurement of insulin concentration, a major cardiovascular risk factor, is not used as a large-scale screening test for insulin resistance. Hence, any test offering an easy method to identify subjects with insulin resistance would be useful. ALT is correlated with insulin resistance and may help in the identification of insulin resistant individuals. In this setting, updated cut-offs of 19 U/l in women and 30 U/l in men may be more appropriate than usual cut-offs (25). Other studies have already assessed the relationship between ALT and insulin resistance, as well as the relationship between ALT and waist circumference. However, the relationship between ALT and insulin resistance should also be assessed taking into account waist circumference, a strong determinant of insulin resistance (26,27).

The main conclusion of this study is that, among subjects with excessive waist circumference, ALT allows for the identification of a subgroup of subjects with a higher risk of insulin resistance: more than 40% of subjects with excessive waist circumference were insulin resistant if ALT was > 19 U/l in women and > 30 U/l in men, and this proportion increased to more than 50% if ALT was > 45 U/l. Hence, in this group of patients, ALT could be used as a tool helping to identify individuals with a higher risk of insulin resistance. By contrast, ALT did not seem useful for the identification of insulin resistant subjects when waist circumference was normal, even if we acknowledge that this conclusion was based on the analysis of a limited number of subjects. Of note, GGT levels were also associated with insulin resistance, presence of metabolic syndrome and excessive waist circumference. In line with this observation, an ALT/AST ratio ≥1 was also associated with insulin resistance, and combining ALT/AST ratio and waist circumference was useful for identifying insulin resistance as well (data not shown). On the other hand, this study confirms that waist circumference is an easy-to-use tool to identify insulin sensitive subjects since excessive waist circumference identified 90% of insulin resistant subjects, which under-

Table 4. — **Sensitivity, specificity, positive and negative predictive values of usual and updated ALT cut-offs for screening for insulin resistance in the whole study group and in individuals with increased and normal waist circumference**

	Whole study group (n=288)	Normal waist circumference (n=70)	Excessive waist circumference (n=218)
Usual ALT cut-offs			
Sensitivity	17 %	12 %	18 %
Specificity	92 %	90 %	93 %
Positive predictive value	47 %	14 %	56 %
Negative predictive value	74 %	89 %	69 %
Updated ALT cut-offs			
Sensitivity	43 %	12 %	47 %
Specificity	70 %	77 %	66 %
Positive predictive value	36 %	7 %	41 %
Negative predictive value	76 %	87 %	71 %

Abbreviations: ALT, alanine aminotransferase

Table 5. — **Usefulness of usual ALT cut-off and waist circumference for identifying insulin resistance**

	Normal waist circumference and normal ALT (n=63)	Normal waist circumference and increased ALT (n=7)	*p*-Value	Excessive waist circumference and normal ALT (n=195)	Excessive waist circumference and increased ALT (n=23)	*p*-Value
HOMA-IR index *	1.1 (1.0-1.2)	2.1 (2.0-2.2)	0.03	2.0 (2.0-2.1)	3.1 (3.0-3.2)	0.02
HOMA-IR index > 2.5 (no. of positive, %)	8 (13%)	1 (14%)	0.9	76 (39%)	15 (65%)	0.02
HOMA-IR index > 3 (no. of positive, %)	7 (11%)	1 (14%)	0.8	60 (31%)	13 (56%)	0.01

* Data expressed as median (95% CI)
Abbreviations: ALT, alanine aminotransferase

Table 6. — **Usefulness of updated ALT cut-offs and waist circumference for identifying insulin resistance**

	Normal waist circumference and normal updated ALT (n=55)	**Normal waist circumference and increased updated ALT (n=15)**	***p*-Value**	**Excessive waist circumference and normal updated ALT (n=135)**	**Excessive waist circumference and increased updated ALT (n=83)**	***p*-Value**
HOMA-IR index *	1.1 (1.0-1.2)	1.9 (1.8-2.0)	0.04	2.0 (1.9-2.0)	2.5 (2.2-2.6)	0.04
HOMA-IR index > 2.5 (no. of positive, %)	8 (14%)	1 (7%)	0.4	50 (37%)	41 (49%)	0.07
HOMA-IR index > 3 (no. of positive, %)	7 (13%)	1 (7%)	0.5	39 (29%)	34 (41%)	0.07

* Data expressed as median (95% CI)
Abbreviations: ALT, alanine aminotransferase

lines that the cardiovascular risk profile should be assessed in patients with increased waist circumference whatever the level of ALT. However, the positive predictive value of excessive waist circumference was low as only one third of subjects with excessive waist circumference were insulin resistant. This study also confirms that normal ALT does not rule out insulin resistance since one fourth of the subjects with normal ALT were insulin resistant, whatever the ALT cut-off used.

Daily intake of small amounts of alcohol is usually considered non detrimental to cardiovascular diseases or to the liver, and sometimes is even considered beneficial. In this study, the main characteristics of participants did not differ between those who abstained from alcohol and those with moderate alcohol intake. Hence, there was no evidence that participants with moderate alcohol intake were protected against liver damage or metabolic factors.

Our study has some limitations, including the limited number of participants, which may explain why the analysis combining waist circumference and updated ALT cut-offs did not reach statistical significance for identifying insulin resistance. This was partly related to very strict selection criteria. We excluded patients with possible confounding factors that might influence outcome, such as antidiabetic medications. In addition, we assessed insulin resistance by the HOMA-IR index. The hyperinsulinemic-euglycemic glucose clamp is the gold standard for measuring insulin sensitivity but it is time consuming, expensive and not feasible in daily practice. The HOMA-IR index, despite being an imperfect assessment of insulin sensitivity, has demonstrated good correlation with hyperinsulinemic-euglycemic glucose clamp and is the most practical test to identify insulin resistance (11,12). In addition, liver steatosis was not assessed. Another limitation was the absence of systematic screening for hepatitis B and C virus infections. However, the prevalence of both infections is rather low in Belgium, below 1% (29-33). Thus, it is unlikely that chronic hepatitis B or C virus infection influenced our results. Finally, our study population cannot be considered as fully representative of the general population as it was a population recruited from pre-operative consultations prior to minor surgery, and this may have influenced the diagnostic accuracy of ALT and waist circumference for identifying insulin resistance. Thus, the conclusions of the present study are only applicable to the study population that has been investigated. However, the perfect selection of reference subjects is impossible (34).

In conclusion, despite being correlated with insulin resistance, ALT seemed not useful for identifying insulin resistance defined by a HOMA-IR index ≥ 3 if waist circumference was ≤80 cm in women and ≤94 cm in men. However, ALT could provide additional help for the identification of subjects with a higher risk of insulin resistance if waist circumference was excessive. One third of the subjects with a waist circumference were insulin resistant; this proportion increased to more than 40% in women with ALT > 19 U/l and men with ALT > 30 U/l and to more than 50% in individuals with ALT > 45 U/l. These results could help to identify subjects presenting undiagnosed insulin resistance that could benefit from further investigations.

Contributorship statement

Sofia Feloni: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Olivier Descamps: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Marie de Vos: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Bénédicte De Vroey: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Hélène Vandenbulcke: acquisition of data; critical revision of the manuscript for important intellectual content

Christopher Doerig: critical revision of the manuscript for important intellectual content

Astrid Marot: critical revision of the manuscript for important intellectual content

Jean Henrion: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Pierre Deltenre: study concept and design, acquisition of data; statistical analysis; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis

Strengths and limitations of the study

– ALT helped for the identification of insulin resistant subjects when waist circumference was abnormal. Among subjects with excessive waist circumference, more than 40% of subjects with excessive waist circumference were insulin resistant if ALT was > 19 U/l in women and > 30 U/l in men, and this proportion increased to more than 50% if ALT was > 45 U/l.

– ALT did not seem useful for the identification of insulin resistant subjects when waist circumference was normal.

– The main limitation of the study is related to the limited number of participants.

– Another limitation of this study is the absence of assessment for liver steatosis.

Compliance with Ethical Standards:

Funding: none

Conflict of Interest: The Drs Sofia Feloni, Olivier Descamps, Marie de Vos, Bénédicte De Vroey, Hélène Vandenbulcke, Christopher Doerig, Astrid Marot, Jean Henrion and Pierre Deltenre declare that they have no conflict of interest

Ethical approval: The study was approved by the Ethical Committee of Jolimont Hospital (Ref. 2008/10) and all procedures are accordance with the 1964 Helsinki declaration and its later amendments. This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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