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LIPID ACCUMULATION PRODUCT OR LAP AS AN UP-TO-DATE CLINICAL BIOCHEMICAL MARKER OF HUMAN OBESITY

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Obesity is a grave medical and social problem causing significant hazards for human health due to frequent occurrence of grave concomitant diseases. Visceral obesity is considered to be the most hazardous. Contemporary diagnostics which allows to reveal visceral obesity both during screening examinations of people who are considered to be conditionally healthy and in patients who suffer from cardiovascular diseases is becoming a very promising trend both in primary and secondary prevention.

The review focuses on an up-to-date marker used to detect visceral obesity, namely, lipid accumulation product or LAP. This index was first introduced by Kahn H.S. in 2005 and is calculated on the basis of two variables, waist circumference (cm) and fasting concentration of triglycerides (mmol/l). When a biochemical and an anthropometric parameter are applied simultaneously to calculate LAP, it allows not only to assess how fats are distributed in a body but also to reflect functional state of fat tissues.

LAP index is widely used as a marker showing there are metabolic disorders in a body (metabolic syndrome, diabetes, resistance to insulin, or nonalcoholic fatty liver disease) and as a cardiovascular diseases predictor. Besides, LAP index, when used to identify obesity phenotype, allows to assign people with overweight into a "metabolically healthy" category or "metabolically ill" one and to reveal patients suffering from metabolic obesity among people with normal body weight. A lot of research revealed that LAP index had a very good diagnostic and predictive potential as regards metabolic and cardiovascular diseases and was a more precise marker of cardio-metabolic risks than conventional anthropometric parameters. The review highlights LAP value ranges, its sex and age peculiarities, as well as a character and an extent to which LAP values change in case of certain diseases. It also dwells on advantages and drawbacks of LAP practical application.

Key words: *lipid accumulation product (LAP), waist circumference, triglycerides, body mass index, obesity, metabolic syndrome, cardiovascular diseases.*

The concept “lipid accumulation product” (LAP) was first mentioned in studies by Kahn H.S. [1, 2] where it was considered as a marker of excessive lipid accumulation in adults. LAP index calculation is based on two simple parameters, waist circumference and triglycerides contents in blood plasma on a fasting. Suggested formulas for LAP index calculation are as follows [3]:

$$\text{LAP for men} = (WC - 65)*TG$$

$$\text{LAP for women} = (WC - 58)*TG,$$

where WC is waist circumference (cm), TG are triglycerides (mmol/l), 65 and 58 are minimal waist circumference for men and women obtained via population research.

A wish to implement LAP index into practices is based on previously published researches [4, 5] when it was determined that increased waist circumference together with elevated triglycerides contents indicated there was a risk of metabolic diseases. However, waist circumference and triglycerides contents were considered to be dichotomous parameters (standard and above standard) in these researches, whereas LAP index calculation allows to obtain qualitative (continuous) values and it gives wider possibilities for analytical processing and interpretation of all obtained data.

LAP index simultaneously describes anatomic and biochemical changes related to excessive lipids accumulation in adults [3].

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An increase in fats contents in a body usually leads to obesity. Obesity is excessive body weight and it is usually assessed as per body mass index (BMI). However, BMI, being a ratio of a person's weight to his or her height, doesn't take into account somatotype, a ratio between fat and muscle weight in a body, and fat tissue distribution; all that significantly decreases its value for an objective overweight evaluation. Thus, a study that was performed on 1,400 people allowed to detect significant discrepancies between results of determining obesity with BMI and x-ray absorptiometry [6].

Unfavorable outcomes that obesity might have are less related to overall fat contents in a body than to peculiarities of its distribution. Basically, there are three types of fat tissue: subcutaneous fat, subfacial fat, and visceral fat. Excessive fat accumulation in the upper part of a body and on the stomach leads to abdominal obesity. In its turn, abdominal obesity is divided into visceral obesity and subcutaneous-abdominal one. Abdominal obesity is thought to be the most hazardous; it usually develops due to excessive increase in visceral fat contents. When such obesity occurs, excessive visceral fat exerts pressure on internal tissues, causes functional disorders in them, and deteriorates blood circulation and lymph flow. Besides, visceral fat tissue differs from subcutaneous fat as per adipocytes type, their endocrine function, lipolytic activity, and sensitivity to insulin and other hormones. Visceral fat tissue, due to its high lipolytic activity, promotes excessive input of free fat acids in big quantities into portal veins and peripheral blood flow; it, in its turn, causes hypertriglyceridemia and atherogenic dyslipidemia, resistance to insulin, hyperglycemia, and hyperinsulinemia [7, 8]. The simplest way to indirectly determine abdominal obesity is to perform anthropometric waist circumference measurement. However, waist circumference measurement doesn't allow determining abdominal obesity type [9, 10], while combine application of waist circumference and triglycerides contents in a formula for LAP index calculation gives an opportunity to apply this index as a marker of metabolic disorders, abdominal-visceral obesity and related diseases.

LAP index in widely used as a marker showing metabolic syndrome [11, 12], resistance to insulin [13, 14], diabetes [15], non-alcoholic fatty liver disease [16, 17], hormonal disorders [18, 19], as well as risk of hypertension [20, 21], stroke [22], renal dysfunction [23, 24], and cardiovascular diseases [25]. The index is also successfully applied to identify people who run high metabolic risks in case of certain diseases (psoriasis, polycystic ovarian disease, and hyposomatotropism) [18, 26, 27]. Besides, researchers revealed a correlation between LAP index and blood lipid profile atherogenicity and lipoproteins sizes [28], blood viscosity [29], blood pressure parameters [30, 31], left ventricle geometry [32], thyreotrophin concentration [33], alcohol intake [34, 35], smoking [36], physical activity [37, 38], alanine aminotransferase level [39], inflammatory biomarkers, and adiponectin [40], and overall mortality as well [41].

LAP index values vary within a wide range. Among population studies, the greatest LAP index variations were detected among Iran population (from 0.62 to 570.26 cm.mmol/l in men (n=3,682) and from 0.56 to 620.39 cm.mmol/l in women (n=4,989)) [42]. Significant variations in LAP index values were also detected among people living in Kenya (from 0 to 388.87 cm.mmol/l in men (n=255) and from 3.30 до 205.54 cm.mmol/l in women (n=273)) [43]; among elderly males in Poland (aged 50–75, n=313) (from 7.36 to 338.97 cm.mmol/l) [19]; and among young women (younger than 40, n=2,810) in Korea (from 0 to 252.0 cm.mmol/l) [44]. However, a significantly wider range of LAP index variations is detected when it comes to patients with cardiovascular pathologies (0.8–1,020 cm.mmol/l in men (n=3,604) and 0.7–1,020 cm.mmol/l in women (n=2,320) respectively) [41].

Table 1

Comparative assessment of LAP index among men and women as per literature data

References	Country	LAP index (cm.mmol/l)				p
		Men		Women		
		M±SD or Me (25%; 75%)	n	M±SD or Me (25%; 75%)	n	
Xia C. et al., 2012 [13]	China	25.96 (14.2; 41.97)	1,510	23.99 (13.09; 40.12)	1,014	0.074
Omuse G. et al., 2017 [43]	Kenya	29.52 (40.95) #	255	23.97 (29.69) #	273	0.055
Wakabayashi I., 2014 [47]	Japan	23.7 (12.1; 44.0)	35,684	16.4 (8.9; 30.1)	18,793	<0.01
Chen Y. et al., 2018 [33]	China	26.69 (34.72)	3,786	22.88 (29.46)	4,941	<0.001
Tripolino C. et al., 2017 [29]	Italy	42.7±28.5	193	29.1±16.1	151	<0.001
Abulmeaty M.M. et al., 2017 [46]	Saudi Arabia	62.17±54.64	167	77.37±60.78	223	0.044
Chiang J.K. et al., 2012 [48]	Taiwan	23.0±23.2	266	28.6±19.3	247	0.001
Wang H. et al., 2018 [32]	China	21.95 (10.71; 43.60)	5,179	28.31 (16.17; 50.95)	6,079	<0.001
Motamed N. et al., 2016 [45]	Iran	47.34±45.55	3,281	58.73±52.86	2,516	<0.001

Note: data are given either as a mean and standard deviation (M±SD), or median and 25% and 75% percentiles (Me (25%; 75%)); # means data are given as median and interquartile spread.

According to some research, LAP index values tend to be higher in men than in women [29, 33], whereas other studies, on the contrary, contain data on higher LAP index values to be more typical for women [45, 46] (Table 1). Some authors state there are no age-related differences in LAP index values [13, 43].

Bearing in mind that the above data differ greatly and are mostly inconsistent, it is impossible to reveal any age-related peculiarities in LAP index changes as per results obtained in various research. Meanwhile, there are only few studies that focus on age dynamics of LAP index changes; besides, they are significantly different as per researches design. I. Wakabayashi [47] performed his research on men (n=35,684) and women (n=18,793) who were divided into four age groups (aged 35–39, 40–49, 50–59 and 60–70). It was detected that LAP index increased with age among women, while its maximum values were detected among men aged 40-49 and then they went down. This ambiguous age dynamics of parameters among men and women resulted in LAP index values being lower among women than among men in younger age groups, but higher in older ones. H.S. Kahn [et al.] [49] gave average LAP index values for two age groups (18–44 and 45–64) that amounted to 28.8 (15.6; 56.6) and 50.2 (30.2; 84.9) cm.mmol/l in men, and 20.8 (11.5; 38.4) and 47.6 (25.3; 82.8) cm.mmol/l in women. Similar age-related dynamics of LAP index values was detected in studies by S.H. Fu [et al.] [50], and H. Joshi [et al.] [51]. Average LAP index among people living in China who were younger than 60 (n=694) amounted to 35.92 (20.33; 61.74) cm.mmol/l; and they significantly grew in people older than 60 (n=846) (p=0.001), up to 41.55 (25.90; 66.13) cm.mmol/l [50]. LAP index amounted to 21.43±14.34 cm.mmol/l in young people (younger than 40, n=1,180) living in India, and it was equal to 31.42±18.11 cm.mmol/l among those older than 40 (n=1,003) [51]. Therefore, basing on the results of all the researches outlined above, we can come to a conclusion that LAP index values, as a rule, tend to increase with age. Obviously, it is due to a fact that waist circumference and triglycerides contents applied for LAP index calculation also tend to go up with age.

A significant number of research that dwells on correlations between LAP index and various diseases focuses on metabolic syndrome. Researchers determined a diagnostic potential (sensitivity, specificity, positive and negative predictive value) of LAP index that could be applied to predict the disease and detected that it was an “ideal” marker to identify metabolic syndrome [45, 48, 52, 53]. Some studies revealed that LAP index predicted metabolic syndrome with greater precision in comparison with anthropometric measurements (BMI or waist circumference) [11, 13, 45, 54]. Nevertheless, some researchers recommend not to overestimate LAP index predictive value as regards metabolic syndrome. When it is calculated, waist circumference and triglycerides contents are applied, but they are also key components in metabolic syndrome and it can determine an internal relation between the index and the disease [55]. Besides, there are data on absence of any advantages LAP index might have against anthropometric parameters for metabolic diseases prediction [56, 57].

Diagnostic precision of LAP index seems to depend on age and sex. Some researchers revealed a greater correlation between LAP index values and risks of diseases among women than among men [47, 58]. Diagnostic precision of LAP index was significantly higher for young people of both sexes than for elderly ones when diabetes and non-alcoholic fatty liver disease were identified [17, 47]. On the contrary, LAP index precision as visceral obesity marker was higher among elderly people [59].

Despite LAP index is widely applied nowadays to assess cardiovascular and metabolic risks, there is no any conventional standard for this index. Researchers, as a rule, calculate optimal threshold LAP index values to predict diseases development basing on ROC-curves (Receiver Operator Characteristic). This procedure allows to determine a threshold value that is the most adequate point for separating one diagnosed group from another. However, optimal threshold LAP index values obtained for each particular disease are different in different studies; it is due to examined populations being different as per sex, age, ethnic groups, and health state of examined people.

Considerable variations are also observed for average LAP index values for different diseases (Table 2).

LAP index is rarely used in Russia. There was a large-scale study entitled “Epidemiology of cardiovascular diseases and risk factors causing thin in the RF regions” (ESSE-RF) that involved LAP index calculating. The study was accomplished in 2012-2014 in 13 regions in Russia by Drapkina O.M. et al, and Shal’nova S.A. et al. There were also some clinical studies (Khripun I.A. et al.; Kornoukhova L.A.). According to data collected via ESSE RF that comprised 20,878 people aged 25-64 (8,058 men and 12,820 women), average LAP index values amounted to 45.5±0.88 and 35.4±0.31 cm.mmol/l among men and women respectively who didn’t have ischemic heart disease or pancreatic diabetes [63–66].

LAP index has an advantage over other anthropometric parameters as it provides a possibility to identify obesity phenotype. Thus, LAP index application allows to divide people with overweight into “metabolically healthy” and “metabolically ill” [67]. At the same time, LAP index enables detecting people with metabolic obesity among those with normal body weight [68].

If a person is healthy but still has metabolic obesity, then excessive fat accumulation in him or her doesn’t lead to unfavorable metabolic effects such as resistance to insulin, disrupted tolerance to dextrose, dyslipidemia, or primary hypertension. As per literature data, prevalence of metabolically healthy obesity in Europe varies from 10% to 45% among people with obesity [69]. Precise diagnostics of obesity phenotype allows to make a correct choice on a set of therapeutic activities aimed at helping a patient to lose weight. At the same time, early detection of

Table 2

Average LAP index values for different diseases as per literature data

References, disease	Country	Sex	LAP index (cm mmol/l)			
			Control		Test	
			M±SD or Me (25%; 75%)	n	M±SD or Me (25%; 75%)	n
Li R. et al., 2018 [12]; metabolic syndrome	China	m+f	21.58±15.04	617	53.47±30.22	375
Cheng Y.L. et al., 2017 [60]; metabolic syndrome	Taiwan	m+f	23.61±18.57	21,233	64.22±43.52	8,564
Mazidi M. et al., 2018 [14]; resistance to insulin	The USA	m+f	53.3±0.6	17,403	127.2±0.5	915
Kavaric N. et al., 2018 [57]; II type pancreatic diabetes	Monte Negro	m+f	44.34 (38.14; 51.53)	119	82.87 (76.69; 90.73)	180
Dai H. et al., 2017 [17]; non-alcoholic fatty liver disease	China	m/f	23.7±22.0 16.6±15.5	10,266 18,043	62.4±59.7 49.4±41.2	8,070 4,080
Wang H. et al., 2017 [61]; ischemic stroke	China	m/f	35.24 (21.78; 42.93) 40.19 (15.93; 49.49)	5,087 5,904	43.49 (29.76; 50.27) 65.21 (31.51; 88.64)	166 188
Li R. et al., 2017 [58]; atherosclerotic stenosis of intracranial vessels	China	m/f	31.73±36.73 37.03±25.65	339 411	32.83±28.74 45.99±37.85	56 39
Wang H. et al., 2018 [21]; hypertension	China	m/f	17.10 (8.45; 34.35) 21.79 (12.86; 38.13)	2,326 3,130	27.46 (13.98; 51.38) 37.27 (21.78; 64.04)	2,732 2,952
Rashid N. et al., 2017 [62]; polycystic ovarian disease	India	m/f	25.77±14.13	45	40.37±22.17	95
Ganguly S. et al., 2018 [26]; psoriasis	India	m+f	23.79±13.02	42	46.42±27.2	40
Chan L. et al., 2016 [18]; hyposomatotropism	China	m+f	21.30 (10.35; 32.48)	75	43.93 (18.74; 69.31)	75

Note: data are given either as a mean and standard deviation (M±SD) or median and 25% and 75% percentiles (Me (25%; 75%)).

"metabolically unhealthy people" with normal body weight can make prediction and prevention of diabetes and cardiovascular diseases much more efficient.

So, LAP index is a marker that reflects joint anatomic and biochemical changes that are related to excessive lipid accumulation in a body. It is an appropriate instrument to detect predisposition to metabolic and cardiovascular diseases. LAP index is easy-to-use, doesn't require any expensive laboratory tests, and should be included into laboratory screening as an early, precise, and cheap metabolic risk predictor. Nevertheless, diagnostic significance, informative values, and possibilities of LAP index application in everyday practices to assess excessive lipids accumulation in a body require further exploration. LAP index has its drawbacks such as low comparability of results obtained in different research, absence of standards for its assessment, and difficulties related to interpreting data at an individual level.

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