Metabolic Syndrome

Chapter 1

Dietary Lipids Linking Postprandial Metabolism and Metabolic Syndrome

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Abstract

The current pandemic of obesity, metabolic syndrome, and type 2 diabetes is intimately associated with an atherogenicdyslipidemic phenotype. The core components of the dyslipidemia of the metabolic syndrome, which most likely initiate atherosclerosis, are the "lipid triad" of high plasma triglycerides, low levels of high-density lipoproteins, and a preponderance of small, dense low-density lipoproteins at fasting. However, postprandial (non-fasting) TG (postprandial hyperlipidemia) are also recognized as an important component for atherosclerosis. Olive oil is the primary source of fat in the Mediterranean diet, which is associated with a significant improvement in health status, as measured by reduced mortality from several chronic diseases. Herein, the purpose of this book chapter was to provide an updateon effects and mechanisms related to the olive oil on postprandial metabolism and its implications for the onset and progression of metabolic syndrome.

Keywords: Olive oil; Postprandial metabolism; Hyperlipidemia; Metabolic syndrome; Lipoproteins

1. Dietary Fatty Acids in Mediterranean Diet

Olive oil plays a pivotal role as the main source of fat in the Mediterranean diet. This diet that has traditionally been linked to longevity in Mediterranean populations and is associated

with a significant improvement in health status, as measured by reduced mortality from several chronic diseases [1]. Virgin olive oils are those obtained from the mesocarp of the drupe from the fruit of the olive tree (Olea europaea L.) [2]. Extra virgin olive oil is a virgin olive oil whose free acidity, expressed as oleic acid, is not more than 0.8 gram per 100 grams and organoleptic characteristics (flavour and colour) are excellent (for olive oil classification and definitions see Ref. [3]). The composition of virgin olive oil includes minor compounds (unsaponifiable fraction) that could range from one to 3% of the oil [4]. The constituents of minor compounds are present in low concentrations but they are responsible for the unique and delicate flavour of virgin olive oil (aldehydes, alcohols, esters, hydrocarbons, ketones, furans, and others). This fraction contains important bioactive compounds.

Fatty acids (FAs) are carboxylic acids and often contain a long, un branched aliphatic chain. FAs are categorized as saturated (SFAs), MUFAs, and polyunsaturated (PUFAs) based on their structural and chemical properties. SFAs do not contain any double bonds or other functional groups along the chain, which is fully saturated with hydrogen atoms. The principal dietary SFAs are palmitic (16:0) and stearic (18:0) acids, which are composed of 16 and 18 carbon atoms, respectively. MUFAs contain one pair of carbon atoms linked by a cis double bond. Oleic acid (18:1n−9), which contains 18 carbon atoms with a double bond at the 9th carbon from the methyl end of the FA molecule, is the major dietary MUFA and represents 55 to 83% of the total FAs in virgin olive oil (Table 1). Carbon chains containing 2 or more cis double bonds, with the first double bond located between either the 3rd and 4th or the 6th and 7th carbon atoms from the methyl end of the FA molecule, belong to the n−3 or n−6, respectively, PUFA families. These families cannot be synthesized by the human body (double bonds can be introduced into all positions of the FA chain with the exception of the n−3 and n−6 positions) and therefore must be obtained from the diet as α-linolenic acid (18:3n−3) and linoleic acid (18:2n−6) or their long-chain PUFA derivatives. Of these FAs, eicosapentaenoic acid (EPA, 20:5n−3), docosahexaenoic acid (DHA, 22:6n−3), dihomo-γ-linolenic acid (20:3n−6), and arachidonic acid (AA, 20:4n−6) are the most metabolically significant [5]. The concentrations of SFAs (palmitic + stearic acids) and PUFAs (α-linolenic + linoleic acids) in virgin olive oil range from 8 to 26% and from 3 to 22% of the total FAs, respectively.

Oleic acid is the primary component of virgin olive oil (≈83% oleic acid in position sn−2 of the triglycerides, TGs) and is also found in peanut oil (≈59% oleic acid) and canola oil (≈37% oleic acid). Oleic acid is a key component of TGs and membrane lipids [6]. Importantly, oleic acid is the most common FA in nature, as well as in our diet (generally, oleic acid supplies an amount of calories equivalent or greater than the amount provided by SFAs and PUFAs combined). Tight restrictions on SFA consumption (<10% of total daily calories; less than 7% for high-risk individuals) and PUFA consumption (<5%) have been recommended. By contrast, oleic acid may provide up to 20–25% of total daily calories.

The unsaponifiable fraction of virgin olive oil contains highly bioactive compounds (>200 constituents) (Table 2). Despite their wide variety and nutritional significance, they commonly account up to 3% of the total oil composition (reaching individual concentrations as smaller as ppm) [7].

Among the several minor compounds of virgin olive oil, the most abundant fraction is hydrocarbons (squalene and, in smaller amounts, the carotenoids β-carotene and lutein). Other minor compounds of virgin olive oil include phytosterols, such as β-sitosterol, Δ5-avenasterol, and campesterol; triterpenic compounds in the form of dialcohols (erythrodiol and uvaol) or acids (oleanolic and maslinic acids); and phenolic compounds, representing the polar fraction [5].

2. Digestion of Triglycerides of Dietary Lipids and Absorption of Fatty Acids

In general, the first event in the transformation of insoluble oil into soluble and absorbable lipids is the formation of an initial emulsion (chyme) by mastication in the mouth where the dispersion of triglycerides (TGs) happens. The surface area of TGs is then increased, which benefits their emulsion (formation of lipid droplets) in the stomach. During the initial gastric process, partially emulsified TGs are attached by lingual and gastric lipases [8]. Gastric lipase activity does not contribute to the hydrolysis of phospholipids (PLs) and cholesteryl esters (CEs), and is functional in the pH range of 3 to 6. In the stomach, this enzyme hydrolyses only 10 to 30% of ingested TGs because of an inhibition process induced by the long-chain free FAs (FFAs) generated, which are mostly protonated at gastric pH. It explains the limited lipolysis of TGs under gastric conditions regarding the complete TGs hydrolysis by pancreatic lipase in the duodenum [9,10]. Absorption of lipid moleculestakes place along the epithelial cells of the small intestine, mainly in the proximal jejunum but also in parts that are more distal. Short-chain (2-4 carbon atoms) and medium-chain (6-12 carbon atoms) FAs are more rapidly absorbed than FAs of more than 14 carbon atoms, because they do not need micellar solubilisation, just bound to albumin and are transported directly to the liver by the portal vein [11].

3. Assembly of Intestinal Lipoproteins Containing Triglycerides from Dietary Lipid Ingestion

In the enterocyte, FFAs from absorption and the pool of endogenous metabolismare used for re-synthesis of TGs. This process is initiated with the activation of FFAs to the corresponding acyl-CoA by acyltransferases. These enzymes form a complex called ''triglyceride synthetase'' [12]. It contributes to 80% of the intestinal TG re-synthesis in the fed state. The composition of these novel TGs closely resembles the composition of TGs from diet [13]. These TGs are coated with cholesterol, PLs, and one molecule of apolipoprotein (apo) B48 at the rough and smooth endoplasmic reticulum in a microsomal TG transfer protein (MTP)-dependent step [14], and

further processed in the Golgi apparatus before being released as chylomicrons (CMs) by the enterocyte through exocytosis. It occurs through the basolateral membrane of enterocytes and CMs enter the lymphatic capillaries of intestinal microvilli that drain into lymphatic channels, reaching the systemic circulation through the thoracic duct [15]. The body can also secrete very low-density lipoproteins (VLDLs). While CMs are of intestinal origin and formed after the ingestion of fatty meals, VLDLs are the major lipoproteins secreted by the liver during fasting [16]. Both CMs and VLDLs are considered TG-rich lipoproteins (TRLs).

4. Postprandial Metabolism

Postprandial hyperlipemia is a normal and transient physiological phenomenon that occurs in response to the ingestion of a fatty meal. Dietary lipids are absorbed as described above and intestinally secreted TRLs have the function to stabilize the absorbed dietary lipids for transport in the aqueous plasma environment and to provide cells with exogenous FAs by receptor (e.g., apoB48 receptor, LDL receptor, and LDL receptor-related protein) or non-receptor-dependent mechanisms for energy and numerous metabolic pathways [17]. In healthy people, the levels of plasma TGs usually peak 3-4 h after a fat meal and tend to return to baseline within 6-8 h. However, postprandial hyperlipemia can become pathological when magnitude and duration of TRL response is exacerbated, resulting in the accumulation of postprandial TRLs and their remnants in the circulation. In that cases, the postprandial hyperlipemic peak may be two to three-fold higher than normal and prolonged, even up to 10-12 h after the dietary fat ingestion [18].

5. Postprandial Metabolism and Metabolic Syndrome

Metabolic syndrome (MetS) is a major and escalating public health and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity, and sedentary life habits. It is estimated that around 20-25% of the world's adult population has MetS. In Spain, a national survey reported that the prevalence of MetS reached up to 30% in 2010 [19]. MetS confers a 5-fold increase in the risk of type-2 diabetes (T2D) and 2-fold the risk of cardiovascular diseases (CVD) over the next 5 to 10 years [20]. Further, patients with MetS are at 2- to 4-fold increased risk of stroke, a 3- to 4-fold increased risk of myocardial infarction (MI), and 2-fold the risk of dying from such events compared with those without MetS [21] regardless of a previous history of cardiovascular problems [22]. MetS is considered as a first order risk factor for atherothrombotic complications and its presence or absence should therefore be considered an indicator of long-term risk.

MetS is defined by a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increase the risk of atherosclerotic CVD, T2D, and all causes of mortality [23,24]. This collection of unhealthy body measurements and abnormal laboratory test outcomes includes atherogenic dyslipidemia, hypertension, glucose intolerance,

and pro-inflammatory and pro-thrombotic states [25,26]. There have been several definitions of MetS, but the most commonly used criteria for definition at present are from the World Health Organization (WHO) [27], the European Group for the study of Insulin Resistance (EGIR) [28], the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) [29], the American Association of Clinical Endocrinologists (AACE) [30], and the International Diabetes Federation (IDF) (Tables 3 and 4).

The core components of the atherogenicdyslipidemia in MetS are the "lipid triad" of high plasma TGs, low levels of HDL-C, and a preponderance of small, dense LDL-C at fasting [32,33]. Several studies have described abnormalities during the postprandial state in patients with CVD [34], showing that non-fasting TGs is an independent predictor of CVD in multivariate analysis [35], even after adjustment for fasting TGs or HDL-C in normolipidemic men. Elevated non-fasting TGs are often found in insulin-resistant subjects. Some reports have indicated that postprandial hyperinsulinemia and/or decreased insulin sensitivity are also involved in altered acute metabolism of dietary fats [36]. We have previously shown that the nature of the dietary fats in the meal influences on postprandial TG concentrations and control of insulin secretion and sensitivity in subjects with normal [37] and high [38] fasting triglyceride concentrations. Our studies provided evidence that subjects had decreased postprandial β-cell function and became less insulin resistant postprandially as the proportion of MUFAs compared with SFAs in dietary fats increased.
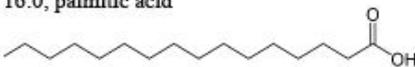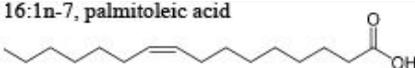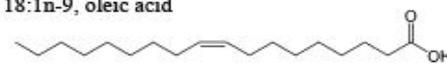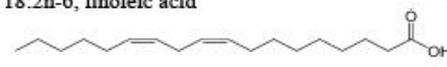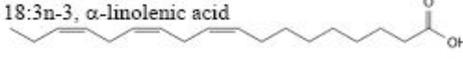
One challenge aspect of MetS is to understand the cellular mechanisms that link the metabolic abnormalities with the pathophysiological effects that generate this disease. One important link has been derived from the finding that pro-inflammatory cytokines are overexpressed during fat abdominal accumulation, which later will lead to several obesity-related disorders [39]. Adipose tissue is a heterogeneous mix of adipocytes, stromal pre-adipocytes, immune cells, and endothelium, which can respond rapidly and dynamically to alterations under nutrient excess through adipocyte hypertrophy and hyperplasia [40]. With obesity and progressive adipocyte enlargement, the blood supplied to adipocytes may be reduced with consequent hypoxia [41]. This condition of inadequate oxygen supply has been proposed to be an inciting aetiology of adipocyte necrosis and macrophage infiltration into adipose tissue, leading to an overproduction of pro-inflammatory factors (e.g., adipokines) and to a local inflammation that propagate an overall systemic inflammation associated with the development of obesity-related comorbidities [42]. Tumour necrosis factor-alpha (TNF-α), adiponectin, visfatin/NAMPT (nicotinamide phosphoribosyltransferase), and interleukin-6 (IL-6) are among the most important adipokines involved in the pathogenesis of MetS and produced by adipocytes and by infiltrated macrophages into adipose tissue [43].

6. Conclusions

MetS is a major and escalating public health and clinical challenge worldwide in the wake of urbanization. The complexity of the molecular pathophysiologyof MetS requires rational therapeutic anddietary strategies. Olive oil is a natural fruit product that contains a unique composition of oleic acid and minorconstituents. Within this context, the consumption of olive oil has shown a broad range of promising activities in the postprandial disturbances. Nonetheless, further efforts are needed to mechanistically define the biochemical and biological postprandial activities of olive oil on atherosclerosis and MetS.

7. Tables

Table 1: Chemical structure and range of major fatty acids in virgin olive oil.

Fatty acid	Regulations[a] (%)
16:0, palmitic acid	7.5-20.0
16:1n-7, palmitoleic acid	0.3-3.5
18:0, stearic acid	0.5-5.0
18:1n-9, oleic acid	55.0-83.0
18:2n-6, linoleic acid	3.5-21.0
18:3n-3, α-linolenic acid	≤ 1.0
MUFA, monounsaturated fatty acids	55-87
SFA, saturated fatty acids	8-26
PUFA, polyunsaturated fatty acids	3-22

[a] International Olive oil council [5]

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Table 2: Minor compounds in virgin olive oil [5].

Minor compounds	Concentration (mg/kg oil)
Squalene	800-8000
β-carotene and lutein	4-10
Sterols	1000-3000
Triterpenic compounds	200-300
Phenols	200-1500
Tocopherols and tocotrienols	250-350

Table 3: Criteria proposed for the clinical diagnosis of MetS [31]

Clinical measures	WHO (1998)	EGIR (1999)	ATP III (2001)
Insulin resistance	IGT, IFG, T2D, or lowered insulin sensitivity plus any 2 of below clinical measures	Plasma insulin >75th percentile	None, but any 3 of below clinical measures
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women
Lipids (at fasting)	TGs ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TGs ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on Rx against hypertension	>130/85 mm Hg
Glucose (at fasting)	IGT, IFG or T2D	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)

Table 4: Criteria proposed for the clinical diagnosis of MetS [31].

Clinical measures	AACE (2003)	IDF (2005)
Insulin resistance	IGT or IFG plus any of below clinical measures	None
Body weight	BMI ≥25 kg/m^2	Increased WC (population specific) plus any 2 of below clinical measures
Lipids (at fasting)	TGs ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL or on Rx against TGs. HDL-C <40 mg/dL in men or <50 mg/dL in women or on Rx to increase HDL-C
Blood pressure	>130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on RX against hypertension
Glucose (at fasting)	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; Rx: receiving treatment; WC: waist circumference.

8. References

1. S. Montserrat-de la Paz, B. Bermudez, M.P. Cardelo, S. Lopez, R. Abia, F.J.G. Muriana. Olive oil and postprandial hyperlipidemia: implications for atherosclerosis and metabolic syndrome. Food Funct., 2016, 7, 4734-4744.

2. S. Lopez, B. Bermudez, S. Montserrat-de la Paz, S. Jaramillo, R. Abia and F.J. Muriana.Virgin olive oil and Hypertension, Curr. Vasc. Pharmacol., 2016, 14, 323-329.

3. B. Bermudez, S. Lopez, A. Ortega, L.M Varela, Y.M. Pacheco, R. Abia and F.J. Muriana. Oleic acid in olive oil: from a metabolic framework toward a clinical perspective, Curr. Pharm. Des., 2011, 17, 831–843.

4. Cardeno, M. Aparicio-Soto, S. Montserrat-de la Paz, B. Bermudez, F.J.G. Muriana and C. Alarcon-de-la-Lastra.

Squalene targets pro- and anti-inflammatory mediators and pathways to modulate over-activation of neutrophils, monocytes and macrophages,J. Funct. Foods, 2015, 14, 779-790.

5. S. Lopez, B. Bermudez, S. Montserrat-de la Paz, S. Jaramillo, L.M. Varela, A. Ortega-Gomez, R. Abia and F.J. Muriana. Membrane composition and dynamics: A target of bioactive virgin olive oil constituents,BBA-Biomembranes, 2014, 1838, 1638-1656.

6. L. Hodson and B.A. Fielding. Stearoyl-CoA desaturase: rogue or innocent bystander? Prog. Lipid. Res., 2013, 52, 15-42.

7. C.A. De la Lastra. An up-date of olive oil and bioactive constituents in health: molecular mechanisms and clinical implications,Curr. Pharm. Des., 2011, 17, 752-753.

8. P.J. Tomasik, A. Wedrychowicz, I. Rogatko, A. Zajac, K. Fyderek and K. Sztefko. Gastric lipase secretion in children with gastritis,Nutrients, 2013, 5, 2924-2932.

9. K. Johnson, L. Ross, R. Miller, X. Xiao and M.E. Lowe. Pancreatic lipase-related protein 2 digests fats in human milk and formula in concert with gastric lipase and carboxyl ester lipase,Pediatr. Res., 2013, 74, 127-132.

10. Y. Pafumi, D. Lairon, P.L. de la Porte, C. Juhel, J. Storch, M. Hamosh and M. Armand. Mechanisms of inhibition of triacylglycerol hydrolysis by human gastric lipase,J. Biol. Chem., 2002, 277, 28070-28079.

11. C.H. Kim, J. Park and M. Kim. Gut microbiota-derived short chain fatty acids, T cells, and inflammation, Immune Netw., 2014, 14, 277-288.

12. F. Wilfling, H. Wang, J.T. Haas, N. Krahmer, T.J. Gould, A. Uchida, J.X. Cheng, M. Graham, R. Chistiano, F. Fröhlich, et al. Triacylglycerol synthesis enzymes mediate lipid droplet growth by relocalizing from ER to lipid droplets,Dev. Cell., 2013, 24, 384-399.

13. Bysted, G. Holmer, P. Lund, B. Sandstrom and T. Tholstrup. Effect of dietary fatty acids on the postprandial fatty acid composition of triacylglycerol-rich lipoproteins in healthy male subjects,Eur. J. Clin. Nutr., 2005, 59, 24-34.

14. Giammanco, A.B. Cefalu, D. Noto and M.R. Averna. The pathophysiology of intestinal lipoprotein production,Front. Physiol., 2015, 6, 61.

15. Bermudez, Y.M. Pacheco, S. Lopez, R. Abia and F.G.M. Muriana. Digestion and absorption of olive oil, Grasas y Aceites, 2004, 55, 1-10.

16. H. Mu and C.E. Hoy. The digestion of dietary triacylglycerols, Prog. Lipid. Res., 2004, 43, 105-133.

17. S. Montserrat-de la Paz, B. Bermudez, M.C. Naranjo, S. Lopez, R. Abia and F.J.G. Muriana. Pharmacological effects of niacin on acute hyperlipemia,Curr. Med. Chem., 2016, 25,2826-2835.

18. J.S. Cohn. Postprandial lipemia and remnant lipoproteins,Clin. Lab. Med., 2006, 26, 773-786.

19. Fernandez-Berges, A. Cabrera de Leon, H. Sanz, R. Elosua, M.J. Guembe, M. Alzamora, T. Vega-Alonso, F.J. Félix-Redondo, H. Ortiz-Marrón, F. Rigo, et al.Metabolic syndrome in Spain: prevalence and coronary risk associated with harmonized definition and WHO proposal. DARIOS study,Rev. Esp. Cardiol., 2012, 65, 241-248.

20. K.G.M.M. Alberti, R.H. Eckel, S.M. Grundy, P.Z. Zimmet, J.I. Cleeman, K.A. Donato, J.C. Fruchart, W.P. James, C.M. Loria, S.C. Jr. Smith, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International atherosclerosis society; And international association for the study of obesity,Circulation, 2009, 120, 1640–1645.

21. K.G.M.M. Alberti, P. Zimmet and J. Shaw. The metabolic syndrome—a new worldwide definition,Lancet,2005, 366, 1059–1062.

22. J.K. Olijhoek, Y. Van Der Graaf, J.D. Banga, A. Algra, T.J. Rabelink and F.L. Visseren. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm,Eur. Heart J., 2004, 25, 342-348.

23. S.M. Grundy, J.I. Cleeman, S.R. Daniels, K.A. Donato, R.H. Eckel, B.A. Franklin, D.J. Gordon, R.M. Krauss, P.J. Savage, S.C. Jr. Smith, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute scientific statement,Circulation, 2005, 112, 2735–2752.

24. P.W.F. Wilson, R.B. D'Agostino, H. Parise, L. Sullivan and J.B. Meigs. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus,Circulation, 2005, 112, 3066–3072.

25. S. Montserrat-de la Paz, M.C. Naranjo, S. Lopez, R. Abia, F.J.G. Muriana and B. Bermudez. Olive oil, compared to a saturated dietary fat, has a protective role on atherosclerosis in niacin-treated mice with metabolic syndrome, J. Funct. Foods, 2016, 26, 557-564.

26. S. Montserrat-de la Paz, M.C. Naranjo, S. Lopez, R. Abia, F.J.G. Muriana and B. Bermudez. Niacin and olive oil promote the skewing to the M2 phenotype in bone marrow-derived macrophages of mice with metabolic syndrome, Food Funct., 2016, 7, 2233-2238.

27. K.G.M.M. Alberti and P.Z. Zimmet. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, Diabetic Med., 1998, 15, 539–553.

28. B. Balkau and M.A. Charles. Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR),Diabetic Med., 1999, 16, 442–443.

29. J.I. Cleeman. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III),J. Am. Med. Assoc., 2001, 285, 2486–2497.

30. Einhorn, G.M. Reaven, R.H. Cobin, E. Ford, O.P. Ganda, Y. Handelsman, R. Hellman, P.S. Jellinger, D. Kendall, R.M. Krauss, et al. American College of Endocrinology position statement on the insulin resistance syndrome, Endocrine Practice, 2003, 9, 237–252.

31. J. Kaur. A comprehensive review on metabolic syndrome, Cardiol. Res. Pract., 2014, 2014, 943162.

32. Emanuela, M. Grazia, de R. Marco, L. Maria Paola, F. Giorgio, B. Marco. Inflammation as a Link between Obesity and Metabolic Syndrome,J. Nutr. Metab.,2012, 2012, 476380.

33. K. Nakajima. Pharmacotherapy of mixed dyslipidemia in the metabolic syndrome,Curr. Clin. Pharmacol., 2010, 5, 133-139.

34. T. Nakamura, J.E. Obata, H. Takano, K. Kawabata, K. Sano, T. Kobayashi, D. Fujioka, Y. Saito, T. Yano and K. Kugiyama.High serum levels of remnant lipoproteins predict ischemic stroke in patients with metabolic syndrome and mild carotid atherosclerosis,Atherosclerosis, 2009, 202, 234-240.

35. B.G. Nordestgaard, A. Langsted and J.J. Freiberg. Nonfastinghyperlipidemia and cardiovascular disease,Curr. Drug Targets, 2009, 10, 328-335.

36. Enkhmaa, Z. Ozturk, E. Anuurad and L. Berglund. Postprandial lipoproteins and cardiovascular disease risk in diabetes mellitus,Curr. Diab. Rep., 2010, 10, 61-69.

37. S. Lopez, B. Bermudez, A. Ortega, L.M. Varela, Y.M. Pacheco, J. Villar, R. Abia and F.J. Muriana. Effects of meals rich in either monounsaturated or saturated fat on lipid concentrations and on insulin secretion and action in subjects with high fasting triglyceride concentrations,Am. J. Clin. Nutr., 2011, 93, 494-499.

38. S. Lopez, B. Bermudez, Y.M. Pacheco, J. Villar, R. Abia and F.J. Muriana. Distinctive postprandial modulation of

beta cell function and insulin sensitivity by dietary fats: monounsaturated compared with saturated fatty acids,Am. J. Clin. Nutr., 2008, 88, 638-644.

39. G.S. Hotamisligil, N.S. Shargill and B.M. Spiegelman. Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance,Science, 1993, 259, 87–91.

40. N. Halberg, I. Wernstedt-Asterholm and P.E. Scherer PE. The adipocyte as an endocrine cell Endocrinology and Metabolism,Clinics of North America, 2008, 37, 753–768.

41. S. Cinti, G. Mitchell, G. Barbatelli, I. Murano, E. Ceresi, E. Faloia, S. Wang, M. Fortier, A.S. Greenberg and M.S. Obin. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans,J. Lipid Res., 2005, 46, 2347–2355.

42. P. Trayhurn and I.S. Wood. Adipokines: inflammation and the pleiotropic role of white adipose tissue,Br. J. Nutr., 2004, 92, 347–355.

43. K. Karastergiou and V. Mohamed-Ali. The autocrine and paracrine roles of adipokines,Mol. Cell Endocrinol., 2010, 318, 69–78.