

Biomarkers of Metabolic Syndrome

Subjects: **Nutrition & Dietetics**

Contributor: Antonio Ruggiero , , Ester Del Vescovo , Silvia Triarico , Giorgio Attinà , Stefano Mastrangelo

The definition of metabolic syndrome (MetS) includes biomarkers such as an increase in triglycerides, a reduction in high-density lipoproteins (HDL), and impaired glucose. However, the alteration of these biomarkers occurs when the condition is already in place; for this reason, it is necessary to identify biomarkers capable of predicting the manifestations related to MetS in advance in order to implement measures to avoid its appearance.

cancer survivors

metabolic syndrome

cardiovascular disease

childhood cancer

obesity

1. Adiponectin

Adiponectin is a protein of 244 amino acids produced by adipocytes and, to a small extent, by cardiac and skeletal myocytes; it is secreted into the bloodstream in three different forms: a trimer, a hexamer, and a high molecular weight multimer ^[1]. The production and secretion of adiponectin is favored by physical exercise and healthy diet, and is different in the two sexes with greater production in the female sex due to the action of estrogen on adipose tissue ^[2]. Once released into the blood, adiponectin binds to transmembrane receptors called AdipoR1, expressed in skeletal muscles, and AdipoR2, expressed by hepatocytes, and acts by modulating numerous metabolic processes ^[1]. At the level of skeletal myocytes, adiponectin increases insulin sensitivity, while in the liver, it up-regulates glucose transport, down-regulates gluconeogenesis and activates the oxidation of fatty acids. Adiponectin also increases insulin sensitivity in the liver, and acts directly on pancreatic cells by increasing insulin secretion ^[3]. Furthermore, adiponectin plays a role in the modulation of inflammatory processes in macrophages, endothelial tissue, muscles and epithelial cells by preventing the production of reactive oxidative species and inhibiting the secretion of hs-CRP. Through these processes, adiponectin acts in a protective way against inflammatory diseases such as atherosclerosis and MetS ^{[4][5]}. In fact, adiponectin inversely correlates with intimal thickness ^{[6][7]} and with adiposity and proinflammatory cytokines; low values of adiponectin, especially of the high molecular weight form, are associated with an increased risk of developing MetS ^[8]. It was shown that adiponectin correlates inversely with adiposity in survivors of brain tumors ^[6], with the antero-posterior diameter of infrarenal abdominal aorta in survivors of leukemia ^[7], and with the appearance of MetS in pediatric survivors of lymphoma and allogeneic hematopoietic stem cell transplantation ^{[9][10]}.

The measurement of adiponectin can be carried out using the enzyme-linked immunosorbent assay (ELISA) technique ^[7]; numerous commercial kits are also available. Erhardt et al. established age- and sex-specific reference values for serum adiponectin in normal-weight 3.0–8.9 year old European children ^[11], and Lausten-Thomsen et al. developed reference levels for total serum adiponectin in children and adolescents aged 6–18 years ^[12]. It is usually expressed in µg/mL.

2. Leptin

Leptin is a 146 amino acid protein encoded by the *ob* gene and released from adipose tissue into the blood in quantities directly proportional to the amount of adipose tissue [13]. Leptin acts to bind a specific receptor present on neuronal, hepatic, pancreatic, cardiac, and perivascular intestinal tissue. At the brain level, leptin has as its main sites of action the solitary tract and the ventral tegmental area in the brain stem, where it reduces appetite by stimulating neurons secreting proopiomelanocortin and inhibiting the orexigenic agouti-related protein/neuropeptide Y-containing (AgRP/NPY) neurons [14]. It also regulates the axes of the thyroid gland, gonads, adrenocorticotrophic hormone and cortisol growth hormone, and changes in cognition, emotions, memory, and the entire brain structure [15][16]. High quantities of leptin are produced in the case of excess adipose tissue, and this determines the inhibition of the sense of hunger and consequent reduction in food intake. Leptin deficiency or resistance is associated with dysregulation of cytokine production, increased susceptibility to infections, autoimmune disorders, malnutrition, and inflammatory responses [14]. The absence of leptin is the cause of a pathological condition characterized by severe obesity, hyperinsulinemia and dyslipidemia [17][18][19]. Leptin plasmatic value is influenced by sex and gender and is greater in females than in males in both children and adults [20]. In adults, leptin is positively correlated with fasting insulin concentrations [21] and is a predictor of glucose intolerance, insulin resistance and MetS regardless of underlying obesity [22]. Furthermore, elevated leptin levels were found to be a significant predictor of cardiovascular-related death and hypertension [23][24]. In children, leptin correlates with the onset of MetS. Madeira et al. demonstrated that in prepubertal children, leptin levels above 13.4 ng/dL were significantly associated with MetS and that, for every 1 ng/dL increase in leptin levels, the odds of MetS increase by 3% [25]. In CCS of brain tumors, plasma leptin values were higher than in healthy subjects and correlate with central fat indicators such as waist-to-hip ratio and waist-to-height ratio [26]. Additionally, in CCS of leukemia and lymphoma and those who survived to hematopoietic stem cell transplantation, leptin levels were demonstrated to be associated with each of the components of MetS [9][27]. The measurement of leptin can be carried out with the ELISA technique, and numerous commercial kits are available. According to Gijón-Conde et al., leptin values that identify cardiometabolic abnormality are 23.75 ng/mL in women and 6.45 ng/mL in men [28]. There is no strong evidence of normal pediatric leptin values [29]. Savino et al. reported that in a group of 317 infants, the median leptin concentration was 2.81 ng/mL in infants younger than 6 months of age, 1.44 ng/mL in infants between 6–12 months of age and 1.77 ng/mL in infants between 12–18 months of age; in addition, they obtained leptin reference values based on age using estimates of the lower and upper percentiles and revealed no gender difference in leptin concentration in early infancy [30]. Instead, Erhardt et al. established age- and sex-specific reference values for serum leptin in normal-weight 3.0–8.9 year old European children [11]. The most frequently used unit of measurement is ng/mL.

3. Uric Acid

Uric acid is the product of purine metabolism, and it is eliminated from the body in part via uric acid transporters present in the kidney and intestinal tract [31], and the remainder is eliminated via the substrate of hypoxanthine-guanine phosphoribosyltransferase, which recycles purines [32]. One of the causes of an increase in uric acid

serum levels is the intake of foods and beverages rich in purines such as meat, seafood, alcohol, and beverages and foods containing high amounts of sugar, such as fructose. Excessive intake of fructose causes the consumption of large quantities of ATP with the production of ADP and AMP, which are metabolized, resulting in the production of uric acid [33][34]. Another cause of hyperuricemia is insulin resistance and high plasma insulin concentrations. In studies carried out on mice, insulin acts at the renal level favoring the expression of the uric acid reabsorption system and decreasing the expression of a major urate secretory transporter [35]. In humans, it was widely demonstrated that insulin values correlate with uric acid values and reduce urinary excretion of uric acid, although the mechanism underlying this phenomenon is not fully known [36][37][38]. The excessive concentration of uric acid in the cells causes an increase in the activity of xanthine oxidase and causes damage to the mitochondria with a consequent increase in the production of reactive oxygen species [39]. Furthermore, uric acid promotes the production of inflammatory cytokines. The production of reactive oxygen species and the activation of the inflammatory system stimulates the well-known process of atherosclerosis, increasing the risk of cardiovascular diseases in subjects with hyperuricemia [39]. Oxidative stress caused by uric acid, in turn, determines an increase in insulin resistance, fatty liver, and dyslipidemia resulting in a vicious circle that causes MetS and an increase in cardiovascular risk [40]. Pluimakers et al. observed that in CCS of abdominal cancer subjected to radiotherapy, uric acid is a predictive indicator of MetS and allows the early identification of subjects at risk of developing it [41]. The same evidence was also obtained in the CCS of allogeneic hemato-poietic stem cell transplantation and leukemia [10][42]. The determination of uric acid in serum can be accomplished using numerous approaches, such as capillary electrophoresis, fluorometry, chromatography, electrochemical methods, chemiluminescence, and colorimetry. The colorimetric method is the most widely used due to its ease of use, high analysis speed, and high sensitivity [43]. In healthy adults, uric acid must be less than 6.6 mg/dL or 360 μ mol/L [44]. Uric acid values are lower in pediatric patients and should be compared with age- and gender-adjusted percentiles [45]. It is usually expressed in mg/dL or μ mol/L.

4. Hs-RCP

Hs-CRP is a pentameric protein synthesized by the liver, whose production is induced by IL-6 during the acute phase of the inflammatory/infectious process. Hs-CRP carries out proinflammatory and also anti-inflammatory activities [46]. It recognizes and promotes the removal of foreign pathogens and damaged cells by binding to phosphocholine, phospholipids, histone, chromatin and fibronectin. Hs-CRP also activates the classical complement pathway and phagocytic cells via immunoglobulin Fc receptors, accelerating the removal of cell debris and damaged or apoptotic cells and foreign pathogens. In some cases, hs-CRP can amplify tissue damage caused by pathogens or autoimmune diseases by activating the complement system, and, therefore, inflammatory cytokines [47][48]. It is also involved in chronic infectious and non-infectious inflammatory processes, and sometimes mild elevations in hs-CRP can be seen without any systemic or inflammatory disease, such as in obesity, insomnia, depression, etc. [46]. Insulin resistance, atherosclerosis, and cardiovascular disease are associated with chronic low levels of systemic inflammation and hs-CRP levels in adults and children [49]. In CCS, exposure to oncogenic insults (chemo- and radiotherapy) induce a persistent activation and recruitment of immune cells, such as lymphocytes and macrophages, determining the production of pro-inflammatory molecules and amplifying the

inflammatory response leading to inflammation, the accumulation of senescent cells, and the increasing of reactive oxygen species and DNA mutations [50][51]. This chronic low-grade inflammation facilitates the onset of MetS in CCS and the general population [52][53]. The close relationship between inflammation and MetS in CCS is evidenced by numerous studies that show correlations between the values of hs-CRP with each of the components of MetS [54][55][56]. The measurement hs-CRP can be performed using immunological tests and laser nephelometry with results reported in mg/dL or mg/L. When used for cardiac risk stratification, hs-CRP levels below 1 mg/L are considered low risk. Levels between 1 mg/L and 3 mg/L are considered moderate risk, and a level above 3 mg/L is deemed to be at high risk for the development of cardiovascular disease [57][58].

5. TNF- α

TNF- α is a cytokine produced by immune and non-immune cells and acts by binding to the receptors of TNFR1 (constitutively and ubiquitously expressed) and TNFR2, which is expressed on lymphocytes and endothelial cells, but can be induced in response to TNFR1 activation and signaling [59]. It is involved in innate and adaptive immunity and in the normal function of immune cells. Sustained and elevated TNF- α production is associated with pathogenic inflammatory disease states, including infection-related sepsis and chronic autoimmune diseases [60]. However, it was seen that TNF- α is abundantly produced in the adipose tissue in obese subjects and that it has a role in mediating insulin resistance [61] and regulating metabolism. TNF- α stimulates hepatic lipid synthesis, and fatty lipolysis in adipose tissue promotes cholesterol and apolipoprotein biosynthesis while decreasing cholesterol catabolism and excretion as bile acids [62]. In addition, TNF- α promotes hypertension, inducing vascular insulin resistance, reducing vasodilation, increasing intravascular fluid and vasoconstriction, and promoting sympathetic overactivity [63]. Being involved in such a large number of processes, TNF- α is one of the fundamental molecules in the pathogenesis of MetS.

In CCS of leukemia, TNF- α was observed to be higher than in controls [64]. Although the crucial role of TNF in the pathogenesis of MetS is evident, there is currently little evidence regarding the usefulness of the assay in CCS [54]. The measurement of TNF- α can be carried out with the ELISA technique, and numerous commercial kits are available. TNF- α values are higher in children than in adults; however, no well-defined reference values for age are available [65]. It is usually expressed in pg/mL.

6. IL-1

IL-1 is a cytokine with a wide range of biological functions, including acting as a leukocytic pyrogen, a mediator of fever and a leukocytic endogenous mediator, and an inducer of several components of the acute-phase response lymphocyte-activating factor [66][67][68]. There are two different isoforms of IL-1, IL-1 α and IL-1 β , which perform the same biological functions [69]. IL-1 α and IL-1 β are produced in a wide variety of cells, especially in macrophages in lymphoid organs. In non-lymphoid organs, IL-1 α and IL-1 β are expressed in tissue macrophages in the lung, digestive tract, liver, glomeruli, and various specific cell types, including neutrophils, epithelial and endothelial cells, lymphocytes, smooth muscle cells and fibroblasts [70][71]. In addition to intervening in the modulation of

inflammatory processes and innate immunity, IL-1 plays a role in the pathogenesis of MetS. High concentrations of glucose and low-density lipoproteins that are produced in the course of MetS are able to favor the production of IL-1 [72][73], and IL-1 α and IL-1 β gene polymorphisms were reported to be associated with central obesity and MetS [74]. Furthermore IL-1, in particular IL-1 β , was observed to have an insulin resistance action; as identified by Spranger et al. in a group of 27,500 subjects, increased plasma IL-1 β , as well as IL-6 levels, increased the risk of developing type 2 diabetes within a 2.3 year period [75]. Necrotic adipocytes release “warning signals” capable of activating the production of IL-1 α , which recruits innate immune cells into adipose tissue. Since adipocyte death is increased in adipose tissue during obesity, IL-1 α plays a pivotal role in the initiation of adipose tissue inflammation during obesity by promoting the chronic inflammation typical of MetS [76][77]. In adults, IL-1 was shown to be highly expressed in several types of tumors, including breast, colon, head and neck, lung, and pancreas tumors, and melanomas [78]. In children with leukemia and a solid tumor, high concentrations of IL-1 were identified [79][80]. However, there is little evidence of the role of IL-1 in the pathogenesis of MetS in CCS [54]. The ELISA technique can be used for the assay of IL-1, and several commercial kits are available. Berdat et al. identified the reference values in relation to the age of the patients [81]. It is usually expressed in pg/mL.

7. IL-6

IL-6 is a 212 amino acids cytokine involved in immune responses and inflammation, hematopoiesis, bone metabolism, embryonic development, and other fundamental processes [82]. It acts on hepatocytes inducing the synthesis of acute-phase proteins such as hs-CRP, serum amyloid A, fibrinogen, and hepcidin, whereas it inhibits albumin production [83]. IL-6 plays an important role in acquired immune response by stimulating antibody production and effector T-cell development. IL-6 stimulates megakaryocytopoiesis in the bone marrow and acts as an osteoclast differentiation modulator [84]. In addition to these functions, IL-6 plays an important role in various metabolic processes as autocrine and/or paracrine actions of adipocyte function [85] and is closely linked to MetS favoring the onset of insulin resistance, elevated glucose production in the liver, inhibition of the insulin-mediated glucose uptake in skeletal muscle, and facilitating the onset of hypertension [86]. Furthermore, the enlargement of adipose tissue in obesity induces mechanical stress and hypoxia in adipocytes, resulting in the release of free fatty acids and inflammatory cytokines such as IL-6 and TNF- α , with the consequent generation of chronic inflammation and amplification of the pathogenetic mechanisms of MetS [87]. It is demonstrated that in adults, IL-6 plays a role in the progression and severity of many forms of cancer [88], and it correlates with poor prognosis in children with neuroblastoma and acute myeloid leukemia [89][90]. Higher IL-6 values were also found in leukemia survivors [64]; however, there is not much evidence for the role of IL-6 in the pathogenesis of MetS in CCS [54]. IL-6 can be assayed using the ELISA technique, as well as several commercial kits. Berdat et al. identified the reference values in relation to the age of the patients [81]. It is usually expressed in pg/mL.

8. ApoB

Apolipoproteins are a group of proteins involved in transport in the various tissues of lipids, which are not soluble in plasma [91]. Among these, apoB is responsible for the transport of chylomicrons, low-density lipoprotein (LDL),

very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and lipoprotein(a) [92]. The same gene encodes two types of apoB: apoB100 is synthesized in the liver and is a component of VLDL and LDL; apoB48 is expressed in the intestine and is present in chylomicrons and their remnants [93]. Of the two forms, apoB100 is the one mainly involved in the formation of atherosclerotic plaques. ApoB48 transports chylomicrons from the intestine to the liver. In the liver, free fatty acids generated from chylomicron residues are used to produce triglycerides incorporated into nascent VLDLs. VLDL particles, each containing a single molecule of apoB100, are secreted by the liver into the blood. VLDL particles shrink with the loss of surface components in HDL and are catabolized into IDL by lipoprotein lipase. Then, IDL is converted to LDL. LDL can be oxidatively modified and absorbed by macrophages, which leads to excessive accumulation and the formation of foam cells which are the initial components of atherosclerotic plaques [94]. At least one apoB molecule is present in all atherosclerotic plaques and for this reason it was proposed as a predictive biomarker of cardiovascular events. In fact, recent studies show that apoB has a higher sensitivity and specificity than LDL in predicting cardiovascular events, such as myocardial infarction in both men and women, independent of age [95]. Patients with high levels of apoB have a higher BMI, waist circumference, systolic blood pressure, fasting insulin and C-reactive protein, which are all components of MetS [96], and epidemiological studies show that apoB predicts the development of type 2 diabetes as much as 3–10 years in advance of clinical onset [97].

Broberg et al. demonstrated high values of apoB in CCS subjected to a high dose of anthracycline [98], and the same observation was shown in CCS of leukemia [99].

The ELISA can measure apoB, but this technique may be expensive and time-consuming, and its accuracy may vary [100]. As an alternative, circulating apoB can be estimated using an algorithm, but these values are only approximations based on lipid variables such as the total cholesterol, HDL or LDL, and triglycerides, and their clinical relevance was not confirmed [101][102]. Yip et al. provided reference interval values for apoB in children and adolescents [103]. It is usually expressed in mg/dL.

9. Lp(a)

Lp(a) is a lipoprotein similar to LDL and contains apo(a) and apoB100 in a 1:1 molar ratio [104]. As with other lipoproteins, it acts as a lipid transporter. It is involved in wound healing by binding to fibrin and thus inhibiting fibrinolysis, and transporting cholesterol to injury sites for cell proliferation during tissue repair [105]. Lp(a), similarly to apoB, is also involved in the formation of atherosclerotic plaques. In fact, it causes the activation of inflammatory and prothrombotic processes, and is involved in the formation of atherosclerotic plaque as it increases the proliferation of smooth muscle cells, increases the formation of foamy cells, increases the necrotic nucleus and calcification of atherosclerotic lesions, and upregulates adhesion molecules [106]. In a group of 56,804 participants, Waldeyer et al. showed that elevated Lp(a) conferred an increased risk for major coronary events and cardiovascular disease [107]. Bermudez et al. showed an association between elevated levels of Lp(a) and the onset of MetS [108]; these data were also confirmed by Paredes et al. [109]. Although the influence exerted by Lp(a) in the genesis of MetS was demonstrated by numerous studies, there is very limited evidence for the role of Lp(a) in the pathogenesis of MetS in CCS [54]. Lp(a) can be measured by immunoassay; it is usually expressed in mg/dL,

but the correct measurement is in nmol/L [\[110\]](#). Langer et al. established the upper percentile cut-offs for Lp(a) as follows: ages 3 to 6 months, 14 mg/dL; ages 6.1 to 12 months, 15 mg/dL; ages 1.1 to 9 years, 22 mg/dL; and ages 9.1 to 18 years, 30 mg/dL [\[111\]](#).

References

1. Achari, A.E.; Jain, S.K. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. *Int. J. Mol. Sci.* 2017, 18, 1321.
2. Khoramipour, K.; Chamari, K.; Hekmatikar, A.A.; Ziyaiyan, A.; Taherkhani, S.; Elguindy, N.M.; Bragazzi, N.L. Adiponectin: Structure, Physiological Functions, Role in Diseases, and Effects of Nutrition. *Nutrients* 2021, 13, 1180.
3. Ramakrishnan, N.; Auger, K.; Jialal, I. Biochemistry, Adiponectin. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2021.
4. Turer, A.T.; Scherer, P.E. Adiponectin: Mechanistic Insights and Clinical Implications. *Diabetologia* 2012, 55, 2319–2326.
5. Devaraj, S.; Torok, N.; Dasu, M.R.; Samols, D.; Jialal, I. Adiponectin Decreases C-Reactive Protein Synthesis and Secretion from Endothelial Cells: Evidence for an Adipose Tissue-Vascular Loop. *Arterioscler. Thromb. Vasc. Biol.* 2008, 28, 1368–1374.
6. Ronsley, R.; Rassekh, S.R.; Fleming, A.; Empringham, B.; Jennings, W.; Portwine, C.; Burrow, S.; Zelcer, S.; Johnston, D.L.; Thabane, L.; et al. High Molecular Weight Adiponectin Levels Are Inversely Associated with Adiposity in Pediatric Brain Tumor Survivors. *Sci. Rep.* 2020, 10, 18606.
7. Giordano, P.; Muggeo, P.; Delvecchio, M.; Carbonara, S.; Romano, A.; Altomare, M.; Ricci, G.; Valente, F.; Zito, A.; Scicchitano, P.; et al. Endothelial Dysfunction and Cardiovascular Risk Factors in Childhood Acute Lymphoblastic Leukemia Survivors. *Int. J. Cardiol.* 2017, 228, 621–627.
8. Nigro, E.; Scudiero, O.; Monaco, M.L.; Palmieri, A.; Mazzarella, G.; Costagliola, C.; Bianco, A.; Daniele, A. New Insight into Adiponectin Role in Obesity and Obesity-Related Diseases. *BioMed Res. Int.* 2014, 2014, 658913.
9. Barbosa-Cortés, L.; López-Alarcón, M.; Mejía-Arangur, J.M.; Klünder-Klünder, M.; Del Carmen Rodríguez-Zepeda, M.; Rivera-Márquez, H.; de la Vega-Martínez, A.; Martín-Trejo, J.; Shum-Luis, J.; Solís-Labastida, K.; et al. Adipokines, Insulin Resistance, and Adiposity as Predictors of Metabolic Syndrome in Child Survivors of Lymphoma and Acute Lymphoblastic Leukemia of a Developing Country. *BMC Cancer* 2017, 17, 125.

10. Bielorai, B.; Weintraub, Y.; Hutt, D.; Hemi, R.; Kanety, H.; Modan-Moses, D.; Goldstein, G.; Hadar, D.; Lerner-Geva, L.; Toren, A.; et al. The Metabolic Syndrome and Its Components in Pediatric Survivors of Allogeneic Hematopoietic Stem Cell Transplantation. *Clin. Transplant.* 2017, 31, e12903.
11. Reference Values for Leptin and Adiponectin in Children below the Age of 10 Based on the IDEFICS Cohort—PubMed. Available online: <https://pubmed.ncbi.nlm.nih.gov/25219410/> (accessed on 6 April 2022).
12. Lausten-Thomsen, U.; Christiansen, M.; Fonvig, C.E.; Trier, C.; Pedersen, O.; Hansen, T.; Holm, J.-C. Reference Values for Serum Total Adiponectin in Healthy Non-Obese Children and Adolescents. *Clin. Chim. Acta* 2015, 450, 11–14.
13. Wasim, M.; Awan, F.R.; Najam, S.S.; Khan, A.R.; Khan, H.N. Role of Leptin Deficiency, Inefficiency, and Leptin Receptors in Obesity. *Biochem. Genet.* 2016, 54, 565–572.
14. Dornbush, S.; Aeddula, N.R. Physiology, Leptin. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
15. Amjad, S.; Baig, M.; Zahid, N.; Tariq, S.; Rehman, R. Association between Leptin, Obesity, Hormonal Interplay and Male Infertility. *Andrologia* 2019, 51, e13147.
16. Farr, O.M.; Gavrieli, A.; Mantzoros, C.S. Leptin Applications in 2015: What Have We Learned about Leptin and Obesity? *Curr. Opin. Endocrinol. Diabetes Obes.* 2015, 22, 353–359.
17. Funcke, J.-B.; von Schnurbein, J.; Lennerz, B.; Lahr, G.; Debatin, K.-M.; Fischer-Posovszky, P.; Wabitsch, M. Monogenic Forms of Childhood Obesity Due to Mutations in the Leptin Gene. *Mol. Cell. Pediatr.* 2014, 1, 3.
18. Farooqi, I.S.; O’Rahilly, S. 20 Years of Leptin: Human Disorders of Leptin Action. *J. Endocrinol.* 2014, 223, T63–T70.
19. Peters, T.; Antel, J.; Föcker, M.; Esber, S.; Hinney, A.; Schéle, E.; Dickson, S.L.; Albayrak, Ö.; Hebebrand, J. The Association of Serum Leptin Levels with Food Addiction Is Moderated by Weight Status in Adolescent Psychiatric Inpatients. *Eur. Eat. Disord. Rev.* 2018, 26, 618–628.
20. Wabitsch, M.; Blum, W.F.; Mucic, R.; Braun, M.; Hube, F.; Rascher, W.; Heinze, E.; Teller, W.; Hauner, H. Contribution of Androgens to the Gender Difference in Leptin Production in Obese Children and Adolescents. *J. Clin. Investig.* 1997, 100, 808–813.
21. Zimmet, P.; Hodge, A.; Nicolson, M.; Staten, M.; de Courten, M.; Moore, J.; Morawiecki, A.; Lubina, J.; Collier, G.; Alberti, G.; et al. Serum Leptin Concentration, Obesity, and Insulin Resistance in Western Samoans: Cross Sectional Study. *BMJ* 1996, 313, 965–969.
22. Franks, P.W.; Brage, S.; Luan, J.; Ekelund, U.; Rahman, M.; Farooqi, I.S.; Halsall, I.; O’Rahilly, S.; Wareham, N.J. Leptin Predicts a Worsening of the Features of the Metabolic Syndrome

- Independently of Obesity. *Obes. Res.* 2005, 13, 1476–1484.
23. Wallace, A.M.; McMahon, A.D.; Packard, C.J.; Kelly, A.; Shepherd, J.; Gaw, A.; Sattar, N. Plasma Leptin and the Risk of Cardiovascular Disease in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 2001, 104, 3052–3056.
 24. Galletti, F.; D’Elia, L.; Barba, G.; Siani, A.; Cappuccio, F.P.; Farinaro, E.; Iacone, R.; Russo, O.; De Palma, D.; Ippolito, R.; et al. High-Circulating Leptin Levels Are Associated with Greater Risk of Hypertension in Men Independently of Body Mass and Insulin Resistance: Results of an Eight-Year Follow-up Study. *J. Clin. Endocrinol. Metab.* 2008, 93, 3922–3926.
 25. Madeira, I.; Bordallo, M.A.; Rodrigues, N.C.; Carvalho, C.; Gazolla, F.; Collett-Solberg, P.; Medeiros, C.; Bordallo, A.P.; Borges, M.; Monteiro, C.; et al. Leptin as a Predictor of Metabolic Syndrome in Prepubertal Children. *Arch. Endocrinol. Metab.* 2017, 61, 7–13.
 26. Sims, E.D.; Jennings, W.J.; Empringham, B.; Fleming, A.; Portwine, C.; Johnston, D.L.; Zelcer, S.M.; Rassekh, S.R.; Burrow, S.; Thabane, L.; et al. Circulating Leptin Levels Are Associated with Adiposity in Survivors of Childhood Brain Tumors. *Sci. Rep.* 2020, 10, 4711.
 27. Annaloro, C.; Usardi, P.; Airaghi, L.; Giunta, V.; Forti, S.; Orsatti, A.; Baldini, M.; Delle Volpe, A.; Lambertenghi Delilieri, G. Prevalence of Metabolic Syndrome in Long-Term Survivors of Hematopoietic Stem Cell Transplantation. *Bone Marrow Transplant.* 2008, 41, 797–804.
 28. Gijón-Conde, T.; Graciani, A.; Guallar-Castillón, P.; Aguilera, M.T.; Rodríguez-Artalejo, F.; Banegas, J.R. Leptin Reference Values and Cutoffs for Identifying Cardiometabolic Abnormalities in the Spanish Population. *Rev. Esp. Cardiol. Engl. Ed.* 2015, 68, 672–679.
 29. Venner, A.A.; Doyle-Baker, P.K.; Lyon, M.E.; Fung, T.S. A Meta-Analysis of Leptin Reference Ranges in the Healthy Paediatric Prepubertal Population. *Ann. Clin. Biochem.* 2009, 46, 65–72.
 30. Savino, F.; Rossi, L.; Benetti, S.; Petrucci, E.; Sorrenti, M.; Silvestro, L. Serum Reference Values for Leptin in Healthy Infants. *PLoS ONE* 2014, 9, e113024.
 31. Joosten, L.A.B.; Crişan, T.O.; Bjornstad, P.; Johnson, R.J. Asymptomatic Hyperuricaemia: A Silent Activator of the Innate Immune System. *Nat. Rev. Rheumatol.* 2020, 16, 75–86.
 32. López-Cruz, R.I.; Crocker, D.E.; Gaxiola-Robles, R.; Bernal, J.A.; Real-Valle, R.A.; Lugo-Lugo, O.; Zenteno-Savín, T. Plasma Hypoxanthine-Guanine Phosphoribosyl Transferase Activity in Bottlenose Dolphins Contributes to Avoiding Accumulation of Non-Recyclable Purines. *Front. Physiol.* 2016, 7, 213.
 33. Zhang, C.; Li, L.; Zhang, Y.; Zeng, C. Recent Advances in Fructose Intake and Risk of Hyperuricemia. *Biomed. Pharmacother.* 2020, 131, 110795.
 34. Li, L.; Zhang, Y.; Zeng, C. Update on the Epidemiology, Genetics, and Therapeutic Options of Hyperuricemia. *Am. J. Transl. Res.* 2020, 12, 3167–3181.

35. Toyoki, D.; Shibata, S.; Kuribayashi-Okuma, E.; Xu, N.; Ishizawa, K.; Hosoyamada, M.; Uchida, S. Insulin Stimulates Uric Acid Reabsorption via Regulating Urate Transporter 1 and ATP-Binding Cassette Subfamily G Member 2. *Am. J. Physiol. Renal Physiol.* 2017, 313, F826–F834.
36. Wang, Y.; Chi, J.; Che, K.; Chen, Y.; Sun, X.; Wang, Y.; Wang, Z. Fasting Plasma Glucose and Serum Uric Acid Levels in a General Chinese Population with Normal Glucose Tolerance: A U-Shaped Curve. *PLoS ONE* 2017, 12, e0180111.
37. MacFarlane, L.A.; Liu, C.-C.; Solomon, D.H. The Effect of Initiating Pharmacologic Insulin on Serum Uric Acid Levels in Patients with Diabetes: A Matched Cohort Analysis. *Semin. Arthritis Rheum.* 2015, 44, 592–596.
38. Mandal, A.K.; Leask, M.P.; Estiverne, C.; Choi, H.K.; Merriman, T.R.; Mount, D.B. Genetic and Physiological Effects of Insulin on Human Urate Homeostasis. *Front. Physiol.* 2021, 12, 713710.
39. Kimura, Y.; Tsukui, D.; Kono, H. Uric Acid in Inflammation and the Pathogenesis of Atherosclerosis. *Int. J. Mol. Sci.* 2021, 22, 12394.
40. King, C.; Lanaspá, M.A.; Jensen, T.; Tolan, D.R.; Sánchez-Lozada, L.G.; Johnson, R.J. Uric Acid as a Cause of the Metabolic Syndrome. *Contrib. Nephrol.* 2018, 192, 88–102.
41. Pluimakers, V.G.; van Waas, M.; Looman, C.W.N.; de Maat, M.P.; de Jonge, R.; Delhanty, P.; Huisman, M.; Mattace-Raso, F.U.S.; van den Heuvel-Eibrink, M.M.; Neggers, S.J.C.M.M. Metabolic Syndrome Detection with Biomarkers in Childhood Cancer Survivors. *Endocr. Connect.* 2020, 9, 676–686.
42. Cheung, Y.T.; Edelmann, M.N.; Mulrooney, D.A.; Green, D.M.; Chemaitilly, W.; John, N.; Robison, L.L.; Hudson, M.M.; Krull, K.R. Uric Acid and Neurocognitive Function in Survivors of Childhood Acute Lymphoblastic Leukemia Treated with Chemotherapy Only. *Cancer Epidemiol. Biomark. Prev.* 2016, 25, 1259–1267.
43. Wang, X.; Chen, S.; Tang, X.; Lin, D.; Qiu, P. Ultrasensitive Detection of Uric Acid in Serum of Patients with Gout by a New Assay Based on Nanoflowers. *RSC Adv.* 2019, 9, 36578–36585.
44. Desideri, G.; Castaldo, G.; Lombardi, A.; Mussap, M.; Testa, A.; Pontremoli, R.; Punzi, L.; Borghi, C. Is It Time to Revise the Normal Range of Serum Uric Acid Levels? *Eur. Rev. Med. Pharmacol. Sci.* 2014, 18, 1295–1306.
45. Luciano, R.; Shashaj, B.; Spreghini, M.; Del Fattore, A.; Rustico, C.; Wietrzykowska Sforza, R.; Morino, G.S.; Dallapiccola, B.; Manco, M. Percentiles of Serum Uric Acid and Cardiometabolic Abnormalities in Obese Italian Children and Adolescents. *Ital. J. Pediatr.* 2017, 43, 3.
46. Nehring, S.M.; Goyal, A.; Patel, B.C. C Reactive Protein. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.

47. Jungen, M.J.; Meulen, B.C.T.; Osch, T.V.; Weinstein, H.C.; Ostelo, R.W.J.G. Inflammatory Biomarkers in Patients with Sciatica: A Systematic Review. *BMC Musculoskelet. Disord.* 2019, 20, 156.
48. Kramer, N.E.; Cosgrove, V.E.; Dunlap, K.; Subramaniapillai, M.; McIntyre, R.S.; Suppes, T. A Clinical Model for Identifying an Inflammatory Phenotype in Mood Disorders. *J. Psychiatr. Res.* 2019, 113, 148–158.
49. Parrett, A.L.; Valentine, R.J.; Arngrímsson, S.A.; Castelli, D.M.; Evans, E.M. Adiposity, Activity, Fitness, and C-Reactive Protein in Children. *Med. Sci. Sports Exerc.* 2010, 42, 1981–1986.
50. Varricchi, G.; Ameri, P.; Cadeddu, C.; Ghigo, A.; Madonna, R.; Marone, G.; Mercurio, V.; Monte, I.; Novo, G.; Parrella, P.; et al. Antineoplastic Drug-Induced Cardiotoxicity: A Redox Perspective. *Front. Physiol.* 2018, 9, 167.
51. Gorini, S.; De Angelis, A.; Berrino, L.; Malara, N.; Rosano, G.; Ferraro, E. Chemotherapeutic Drugs and Mitochondrial Dysfunction: Focus on Doxorubicin, Trastuzumab, and Sunitinib. *Oxid. Med. Cell. Longev.* 2018, 2018, 7582730.
52. Muhic, E.; Mathiesen, S.; Nielsen, M.M.; Suominen, A.; Sørensen, K.; Ifversen, M.; Nolsøe, R.L.; Pedersen, K.M.; Lähteenmäki, P.; Nordestgaard, B.G.; et al. Metabolic Syndrome in Male Survivors of Pediatric Allogeneic Hematopoietic Stem Cell Transplantation: Impact of Total Body Irradiation, Low-Grade Inflammation, and Hypogonadism. *Transplant. Cell. Ther.* 2021, 27, 778.e1–778.e8.
53. Turcotte, L.M.; Yingst, A.; Verneris, M.R. Metabolic Syndrome after Hematopoietic Cell Transplantation: At the Intersection of Treatment Toxicity and Immune Dysfunction. *Biol. Blood Marrow Transplant.* 2016, 22, 1159–1166.
54. Pluimakers, V.G.; van Santen, S.S.; Fiocco, M.; Bakker, M.-C.E.; van der Lelij, A.J.; van den Heuvel-Eibrink, M.M.; Neggers, S.J.C.M.M. Can Biomarkers Be Used to Improve Diagnosis and Prediction of Metabolic Syndrome in Childhood Cancer Survivors? A Systematic Review. *Obes. Rev.* 2021, 22, e13312.
55. Cepelova, M.; Kruseova, J.; Luks, A.; Capek, V.; Cepela, P.; Potockova, J.; Kraml, P. Accelerated Atherosclerosis, Hyperlipoproteinemia and Insulin Resistance in Long-Term Survivors of Hodgkin Lymphoma during Childhood and Adolescence. *Neoplasma* 2019, 66, 978–987.
56. Felicetti, F.; Cento, A.S.; Fornengo, P.; Cassader, M.; Mastrocola, R.; D'Ascenzo, F.; Settanni, F.; Benso, A.; Arvat, E.; Collino, M.; et al. Advanced Glycation End Products and Chronic Inflammation in Adult Survivors of Childhood Leukemia Treated with Hematopoietic Stem Cell Transplantation. *Pediatr. Blood Cancer* 2020, 67, e28106.
57. Lee, Y.; McKechnie, T.; Doumouras, A.G.; Handler, C.; Eskicioglu, C.; Gmora, S.; Anvari, M.; Hong, D. Diagnostic Value of C-Reactive Protein Levels in Postoperative Infectious Complications

- After Bariatric Surgery: A Systematic Review and Meta-Analysis. *Obes. Surg.* 2019, 29, 2022–2029.
58. Johns, I.; Moschonas, K.E.; Medina, J.; Ossei-Gerning, N.; Kassianos, G.; Halcox, J.P. Risk Classification in Primary Prevention of CVD According to QRISK2 and JBS3 'Heart Age', and Prevalence of Elevated High-Sensitivity C Reactive Protein in the UK Cohort of the EURIKA Study. *Open Heart* 2018, 5, e000849.
 59. Medler, J.; Wajant, H. Tumor Necrosis Factor Receptor-2 (TNFR2): An Overview of an Emerging Drug Target. *Expert Opin. Ther. Targets* 2019, 23, 295–307.
 60. Sethi, J.K.; Hotamisligil, G.S. Metabolic Messengers: Tumour Necrosis Factor. *Nat. Metab.* 2021, 3, 1302–1312.
 61. Mathis, D.; Shoelson, S.E. Immunometabolism: An Emerging Frontier. *Nat. Rev. Immunol.* 2011, 11, 81–83.
 62. Feingold, K.R.; Soued, M.; Staprans, I.; Gavin, L.A.; Donahue, M.E.; Huang, B.J.; Moser, A.H.; Gulli, R.; Grunfeld, C. Effect of Tumor Necrosis Factor (TNF) on Lipid Metabolism in the Diabetic Rat. Evidence That Inhibition of Adipose Tissue Lipoprotein Lipase Activity Is Not Required for TNF-Induced Hyperlipidemia. *J. Clin. Investig.* 1989, 83, 1116–1121.
 63. Yanai, H.; Tomono, Y.; Ito, K.; Furutani, N.; Yoshida, H.; Tada, N. The Underlying Mechanisms for Development of Hypertension in the Metabolic Syndrome. *Nutr. J.* 2008, 7, 10.
 64. Ariffin, H.; Azanan, M.S.; Abd Ghafar, S.S.; Oh, L.; Lau, K.H.; Thirunavakarasu, T.; Sedan, A.; Ibrahim, K.; Chan, A.; Chin, T.F.; et al. Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia Show Evidence of Chronic Inflammation and Cellular Aging. *Cancer* 2017, 123, 4207–4214.
 65. Decker, M.-L.; Grobusch, M.P.; Ritz, N. Influence of Age and Other Factors on Cytokine Expression Profiles in Healthy Children—A Systematic Review. *Front. Pediatr.* 2017, 5, 255.
 66. Kaneko, N.; Kurata, M.; Yamamoto, T.; Morikawa, S.; Masumoto, J. The Role of Interleukin-1 in General Pathology. *Inflamm. Regen.* 2019, 39, 12.
 67. Gery, I.; Gershon, R.K.; Waksman, B.H. Potentiation of the T-Lymphocyte Response to Mitogens. I. The Responding Cell. *J. Exp. Med.* 1972, 136, 128–142.
 68. Rosenstreich, D.L.; Vogel, S.N.; Jacques, A.R.; Wahl, L.M.; Oppenheim, J.J. Macrophage Sensitivity to Endotoxin: Genetic Control by a Single Codominant Gene. *J. Immunol.* 1978, 121, 1664–1670.
 69. Lachman, L.B.; Hacker, M.P.; Handschumacher, R.E. Partial Purification of Human Lymphocyte-Activating Factor (LAF) by Ultrafiltration and Electrophoretic Techniques. *J. Immunol.* 1977, 119, 2019–2023.

70. Takács, L.; Kovacs, E.J.; Smith, M.R.; Young, H.A.; Durum, S.K. Detection of IL-1 Alpha and IL-1 Beta Gene Expression by in Situ Hybridization. Tissue Localization of IL-1 mRNA in the Normal C57BL/6 Mouse. *J. Immunol.* 1988, 141, 3081–3095.
71. Dinarello, C.A. The Interleukin-1 Family: 10 Years of Discovery. *FASEB J.* 1994, 8, 1314–1325.
72. Maedler, K.; Sergeev, P.; Ris, F.; Oberholzer, J.; Joller-Jemelka, H.I.; Spinas, G.A.; Kaiser, N.; Halban, P.A.; Donath, M.Y. Glucose-Induced Beta Cell Production of IL-1 β Contributes to Glucotoxicity in Human Pancreatic Islets. *J. Clin. Investig.* 2002, 110, 851–860.
73. Böni-Schnetzler, M.; Boller, S.; Debray, S.; Bouzakri, K.; Meier, D.T.; Prazak, R.; Kerr-Conte, J.; Pattou, F.; Ehses, J.A.; Schuit, F.C.; et al. Free Fatty Acids Induce a Proinflammatory Response in Islets via the Abundantly Expressed Interleukin-1 Receptor I. *Endocrinol.* 2009, 150, 5218–5229.
74. Carter, K.W.; Hung, J.; Powell, B.L.; Wiltshire, S.; Foo, B.T.X.; Leow, Y.C.; McQuillan, B.M.; Jennens, M.; McCaskie, P.A.; Thompson, P.L.; et al. Association of Interleukin-1 Gene Polymorphisms with Central Obesity and Metabolic Syndrome in a Coronary Heart Disease Population. *Hum. Genet.* 2008, 124, 199–206.
75. Spranger, J.; Kroke, A.; Möhlig, M.; Hoffmann, K.; Bergmann, M.M.; Ristow, M.; Boeing, H.; Pfeiffer, A.F.H. Inflammatory Cytokines and the Risk to Develop Type 2 Diabetes: Results of the Prospective Population-Based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes* 2003, 52, 812–817.
76. Ballak, D.B.; Stienstra, R.; Tack, C.J.; Dinarello, C.A.; van Diepen, J.A. IL-1 Family Members in the Pathogenesis and Treatment of Metabolic Disease: Focus on Adipose Tissue Inflammation and Insulin Resistance. *Cytokine* 2015, 75, 280–290.
77. Cinti, S.; Mitchell, G.; Barbatelli, G.; Murano, I.; Ceresi, E.; Faloia, E.; Wang, S.; Fortier, M.; Greenberg, A.S.; Obin, M.S. Adipocyte Death Defines Macrophage Localization and Function in Adipose Tissue of Obese Mice and Humans. *J. Lipid Res.* 2005, 46, 2347–2355.
78. Bent, R.; Moll, L.; Grabbe, S.; Bros, M. Interleukin-1 Beta—A Friend or Foe in Malignancies? *Int. J. Mol. Sci.* 2018, 19, 2155.
79. Chybicka, A.; Bogusławska-Jaworska, J. Interleukin-1 Production in Childhood Acute Lymphoblastic Leukemia during Chemo- and Radiotherapy According to BFM (Berlin-Frankfurt-Münster) Protocol. *Haematol. Blood Transfus.* 1990, 33, 72–75.
80. Bomfim, E.D.O.; Anatriello, E.; Nunes, M.D.R.; Moraes, J.C.; Cintra, M.M.; Lopes-Junior, L.C.; Miyauti, M.; Nascimento, L.C.; de Lima, R.A.G.; Floria-Santos, M. Correlations between Functional Interleukin-1 and Changes in Fatigue and Quality of Life in Children and Adolescents with Cancer. *J. Clin. Oncol.* 2015, 33.
81. Berdat, P.A.; Wehrle, T.J.; Küng, A.; Achermann, F.; Sutter, M.; Carrel, T.P.; Nydegger, U.E. Age-Specific Analysis of Normal Cytokine Levels in Healthy Infants. *Clin. Chem. Lab. Med.* 2003, 41,

1335–1339.

82. Hirano, T. IL-6 in Inflammation, Autoimmunity and Cancer. *Int. Immunol.* 2021, 33, 127–148.
83. Tanaka, T.; Narazaki, M.; Kishimoto, T. IL-6 in Inflammation, Immunity, and Disease. *Cold Spring Harb. Perspect. Biol.* 2014, 6, a016295.
84. Harmer, D.; Falank, C.; Reagan, M.R. Interleukin-6 Interweaves the Bone Marrow Microenvironment, Bone Loss, and Multiple Myeloma. *Front. Endocrinol.* 2018, 9, 788.
85. Testa, R.; Olivieri, F.; Bonfigli, A.R.; Sirolla, C.; Boemi, M.; Marchegiani, F.; Marra, M.; Cenerelli, S.; Antonicelli, R.; Dolci, A.; et al. Interleukin-6-174 G > C Polymorphism Affects the Association between IL-6 Plasma Levels and Insulin Resistance in Type 2 Diabetic Patients. *Diabetes Res. Clin. Pract.* 2006, 71, 299–305.
86. Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z. The Metabolic Syndrome. *Lancet* 2005, 365, 1415–1428.
87. Obesity-Induced TNF α and IL-6 Signaling: The Missing Link between Obesity and Inflammation-Driven Liver and Colorectal Cancers—PubMed. Available online: <https://pubmed.ncbi.nlm.nih.gov/30591653/> (accessed on 6 April 2022).
88. Tian, G.; Mi, J.; Wei, X.; Zhao, D.; Qiao, L.; Yang, C.; Li, X.; Zhang, S.; Li, X.; Wang, B. Circulating Interleukin-6 and Cancer: A Meta-Analysis Using Mendelian Randomization. *Sci. Rep.* 2015, 5, 11394.
89. Egler, R.A.; Burlingame, S.M.; Nuchtern, J.G.; Russell, H.V. Interleukin-6 and Soluble Interleukin-6 Receptor Levels as Markers of Disease Extent and Prognosis in Neuroblastoma. *Clin. Cancer Res.* 2008, 14, 7028–7034.
90. Stevens, A.M.; Miller, J.M.; Munoz, J.O.; Gaikwad, A.S.; Redell, M.S. Interleukin-6 Levels Predict Event-Free Survival in Pediatric AML and Suggest a Mechanism of Chemotherapy Resistance. *Blood Adv.* 2017, 1, 1387–1397.
91. Jialal, I.; Barton Duell, P. Diagnosis of Familial Hypercholesterolemia. *Am. J. Clin. Pathol.* 2016, 145, 437–439.
92. Devaraj, S.; Semaan, J.R.; Jialal, I. Biochemistry, Apolipoprotein B. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
93. Nakajima, K.; Nakano, T.; Tokita, Y.; Nagamine, T.; Inazu, A.; Kobayashi, J.; Mabuchi, H.; Stanhope, K.L.; Havel, P.J.; Okazaki, M.; et al. Postprandial Lipoprotein Metabolism: VLDL vs Chylomicrons. *Clin. Chim. Acta* 2011, 412, 1306–1318.
94. Behbodikhah, J.; Ahmed, S.; Elyasi, A.; Kasselmann, L.J.; De Leon, J.; Glass, A.D.; Reiss, A.B. Apolipoprotein B and Cardiovascular Disease: Biomarker and Potential Therapeutic Target. *Metabolites* 2021, 11, 690.

95. Walldius, G.; Jungner, I.; Holme, I.; Aastveit, A.H.; Kolar, W.; Steiner, E. High Apolipoprotein B, Low Apolipoprotein A-I, and Improvement in the Prediction of Fatal Myocardial Infarction (AMORIS Study): A Prospective Study. *Lancet* 2001, 358, 2026–2033.
96. Williams, K.; Sniderman, A.D.; Sattar, N.; D'Agostino, R., Jr.; Wagenknecht, L.E.; Haffner, S.M. Comparison of the Associations of Apolipoprotein B and Low-Density Lipoprotein Cholesterol with Other Cardiovascular Risk Factors in the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2003, 108, 2312–2316.
97. Salomaa, V.; Havulinna, A.; Saarela, O.; Zeller, T.; Jousilahti, P.; Jula, A.; Muenzel, T.; Aromaa, A.; Evans, A.; Kuulasmaa, K.; et al. Thirty-One Novel Biomarkers as Predictors for Clinically Incident Diabetes. *PLoS ONE* 2010, 5, e10100.
98. Broberg, O.; Øra, I.; Wiebe, T.; Weismann, C.G.; Liuba, P. Characterization of Cardiac, Vascular, and Metabolic Changes in Young Childhood Cancer Survivors. *Front. Pediatr.* 2021, 9, 764679.
99. Morel, S.; Leahy, J.; Fournier, M.; Lamarche, B.; Garofalo, C.; Grimard, G.; Poulain, F.; Delvin, E.; Laverdière, C.; Krajcinovic, M.; et al. Lipid and Lipoprotein Abnormalities in Acute Lymphoblastic Leukemia Survivors. *J. Lipid Res.* 2017, 58, 982–993.
100. Cao, J.; Steffen, B.T.; Guan, W.; Remaley, A.T.; McConnell, J.P.; Palamalai, V.; Tsai, M.Y. A Comparison of Three Apolipoprotein B Methods and Their Associations with Incident Coronary Heart Disease Risk over a 12-Year Follow-up Period: The Multi-Ethnic Study of Atherosclerosis. *J. Clin. Lipidol.* 2018, 12, 300–304.
101. Hermans, M.P.; Sacks, F.M.; Ahn, S.A.; Rousseau, M.F. Non-HDL-Cholesterol as Valid Surrogate to Apolipoprotein B100 Measurement in Diabetes: Discriminant Ratio and Unbiased Equivalence. *Cardiovasc. Diabetol.* 2011, 10, 20.
102. Hwang, Y.-C.; Ahn, H.-Y.; Lee, W.J.; Park, C.-Y.; Park, S.-W. An Equation to Estimate the Concentration of Serum Apolipoprotein B. *PLoS ONE* 2012, 7, e51607.
103. Yip, P.M.; Chan, M.K.; Nelken, J.; Lepage, N.; Brotea, G.; Adeli, K. Pediatric Reference Intervals for Lipids and Apolipoproteins on the VITROS 5,1 FS Chemistry System. *Clin. Biochem.* 2006, 39, 978–983.
104. Albers, J.J.; Kennedy, H.; Marcovina, S.M. Evidence That Lp Contains One Molecule of Apo and One Molecule of ApoB: Evaluation of Amino Acid Analysis Data. *J. Lipid Res.* 1996, 37, 192–196.
105. Brown, M.S.; Goldstein, J.L. Plasma Lipoproteins: Teaching Old Dogmas New Tricks. *Nature* 1987, 330, 113–114.
106. Saeed, A.; Virani, S.S. Lipoprotein(a) and Cardiovascular Disease: Current State and Future Directions for an Enigmatic Lipoprotein. *Front. Biosci. Landmark Ed.* 2018, 23, 1099–1112.

107. Waldeyer, C.; Makarova, N.; Zeller, T.; Schnabel, R.B.; Brunner, F.J.; Jørgensen, T.; Linneberg, A.; Niiranen, T.; Salomaa, V.; Jousilahti, P.; et al. Lipoprotein(a) and the Risk of Cardiovascular Disease in the European Population: Results from the BiomarCaRE Consortium. *Eur. Heart J.* 2017, 38, 2490–2498.
108. Bermúdez, V.; Rojas, J.; Salazar, J.; Bello, L.; Añez, R.; Toledo, A.; Chacín, M.; Aguirre, M.; Villalobos, M.; Chávez, M.; et al. Variations of Lipoprotein(a) Levels in the Metabolic Syndrome: A Report from the Maracaibo City Metabolic Syndrome Prevalence Study. *J. Diabetes Res.* 2013, 2013, 416451.
109. Paredes, S.; Fonseca, L.; Ribeiro, L.; Ramos, H.; Oliveira, J.C.; Palma, I. Novel and Traditional Lipid Profiles in Metabolic Syndrome Reveal a High Atherogenicity. *Sci. Rep.* 2019, 9, 11792.
110. Cegla, J.; France, M.; Marcovina, S.M.; Neely, R.D.G. Lp(a): When and How to Measure It. *Ann. Clin. Biochem.* 2021, 58, 16–21.
111. Langer, C.; Tambyrayah, B.; Thedieck, S.; Nowak-Göttl, U. Testing for Lipoprotein(a) Concentration and Apolipoprotein(a) Phenotypes: Method Standardization and Pediatric Reference Values. *Semin. Thromb. Hemost.* 2011, 37, 810–813.

Retrieved from <https://encyclopedia.pub/entry/history/show/57224>