Journal of *Personalized Medicine*

MDPI

Review

Biomarkers Predictive of Metabolic Syndrome and Cardiovascular Disease in Childhood Cancer Survivors

Alberto Romano, Ester Del Vescovo, Serena Rivetti, Silvia Triarico, Giorgio Attinà, Stefano Mastrangelo, Palma Maurizi and Antonio Ruggiero *

Pediatric Oncology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica Sacro Cuore, 00168 Rome, Italy; alberto.romano@guest.policlinicogemelli.it (A.R.); esterdelvescovo@gmail.com (E.D.V.); serena.rivetti@gmail.com (S.R.); silvia.triarico@guest.policlinicogemelli.it (S.T.); giorgio.attina@policlinicogemelli.it (G.A.); stefano.mastrangelo@unicatt.it (S.M.); palma.maurizi@unicatt.it (P.M.)
* Correspondence: antonio.ruggiero@unicatt.it; Tel.: +39-06-3058203; Fax: +39-06-3052751

Abstract: The improvement in childhood cancer treatments resulted in a marked improvement in the survival of pediatric cancer patients. However, as survival increased, it was also possible to observe the long-term side effects of cancer therapies. Among these, metabolic syndrome is one of the most frequent long-term side effects, and causes high mortality and morbidity. Consequently, it is necessary to identify strategies that allow for early diagnosis. In this review, the pathogenetic mechanisms of metabolic syndrome and the potential new biomarkers that can facilitate its diagnosis in survivors of pediatric tumors are analyzed.

Keywords: cancer survivors; metabolic syndrome; cardiovascular disease; childhood cancer; chemotherapy toxicity; radiotherapy toxicity; obesity

Citation: Romano, A.; Del Vescovo, E.; Rivetti, S.; Triarico, S.; Attinà, G.; Mastrangelo, S.; Maurizi, P.; Ruggiero, A. Biomarkers Predictive of Metabolic Syndrome and Cardiovascular Disease in Childhood Cancer Survivors. *J. Pers. Med.* **2022**, *12*, 880. https://doi.org/10.3390/jpm12060880

Academic Editors: Umberto Basile and Ettore Domenico Capoluongo

Received: 17 April 2022
Accepted: 25 May 2022
Published: 27 May 2022

1. Introduction

In recent years, the improvement in childhood cancer treatments and the adoption of international cooperative treatment regimens, which permit the combination of surgery, radiotherapy and chemotherapy, resulted in a marked increase in survival [1,2]. In parallel with the increase in survival, increased toxicity was observed, and treatment-related long-term side effects were noted [3,4]. Chemotherapy, high-dose steroid therapy and radiotherapy cause long-term toxic effects on numerous organs, including the kidneys, heart, endocrine system, and ear [5–7]. These treatments are also the cause of chronic inflammation and metabolic alterations, resulting in the onset of metabolic syndrome (MetS) and consequent increase in cardiovascular risk [8]. Cardiovascular-related death is seven times more frequent in childhood cancer survivors (CCS) than in the general population. It is the cause of a quarter of all deaths within 45 years of cancer diagnosis [9]. Such a high incidence explains the need to carry out careful monitoring of CCS to diagnose the onset of MetS early and implement measures aimed at reducing the risk of cardiovascular-related death. This review analyzes the pathogenetic mechanisms underlying the onset of MetS and cardiovascular diseases in CCS and the new biomarkers that allow them to be diagnosed early.

Research Methods

This research aimed to write an integrative review to summarize the knowledge currently available on the pathogenesis of MetS and cardiovascular diseases in CCS and their new diagnostic biomarkers. To reach this goal, we searched for papers dedicated to biomarkers of MetS and cardiovascular diseases in CCS, and performed a Pubmed-based retrieval of articles using the search terms "Metabolic syndrome", "Cardiovascular risk" and "biomarkers" matched with "cancer survivors" and "biomarkers". After the original search, we used filters to select articles available in the English language and articles with

available full texts. This research retrieved 220 articles. Two operators set the 220 articles according to the adherence of the title and abstract to the topic.

The literature review was later expanded to search for single biomarkers matched to "cancer survivors" filtered to select articles available in the English language and articles with available full texts. This research retrieved 47 articles that the same two operators analyzed.

A total of 150 papers were obtained and included in the review at the end of this search.

Figure 1 summarizes the research methods.

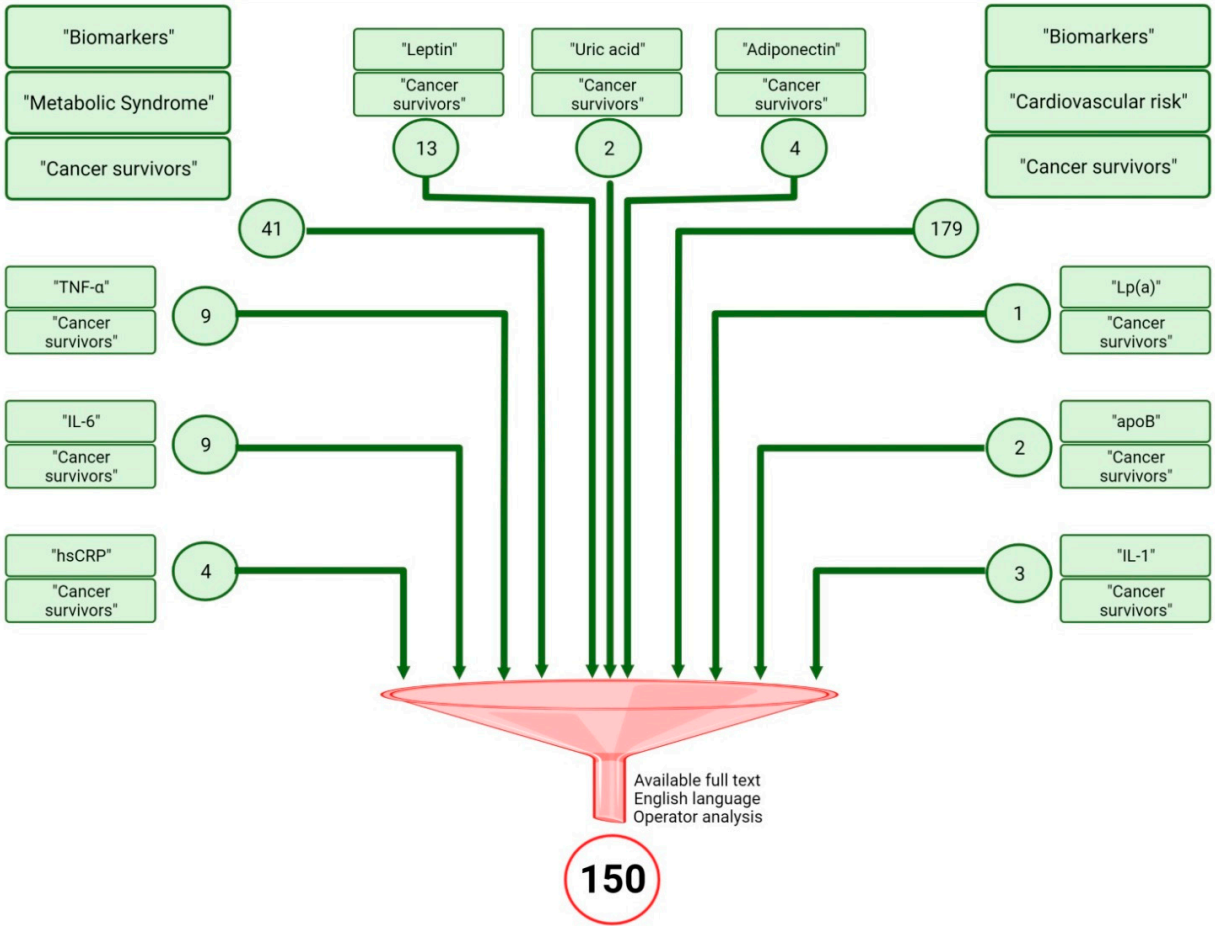

Figure 1. Research methods. The figure shows the results of the research carried out on PubMed. The rectangles contain the search terms. The number of articles obtained from the individual searches are contained in the circles. All articles obtained were analyzed according to the filters noted adjacent to the funnel. The final number of articles included in the review is 149.

2. Pathogenesis of Metabolic Syndrome and Cardiovascular Disease in CCS

MetS is a group of symptoms that includes obesity, impaired glucose tolerance and dyslipidemia. It is also characterized by inflammatory and prothrombotic states [10,11]. Many definitions describe MetS, but the latest consensus of the International Diabetes Federation, the National Heart, Lung and Blood Institute and the American Heart Association, in 2009, defined diagnostic criteria to diagnose MetS for adult patients [12,13]. At least three of the following are required to diagnose MetS:

- Raised Waist Circumference (population- and country-specific definitions)
- Fasting Plasma Glucose Concentration $\geq$ 100 mg/dL or on diabetes treatment
- Blood Pressure $\geq$ 130/85 mmHg, or on antihypertensive treatment
- Triglycerides $\geq$ 150 mg/dL or on treatment

- High-density lipoprotein cholesterol < 40 mg/dL in men and < 50 mg/dL in women, or on treatment.

On the other hand, pediatric patients have no univocal guidelines for the diagnosis of MetS. The definitions available now share the following criteria: central obesity, hypertension, hypertriglyceridemia, low HDL, and impaired glucose [14].

CCS have an increased risk of developing MetS compared to their siblings, and a 10 times higher risk of developing cardiovascular disease [15]. The pathogenesis of MetS in CCS is not well known. Still, many studies underline the role of low-grade chronic inflammation due to cytokine activation released from abdominal fat determined by the direct action of treatments on organs and the cardiovascular system. Radiotherapy, chemotherapy and prolonged, high-dose steroid therapy can interfere with metabolic processes, facilitating the onset of MetS [16].

2.1. Radiotherapy

Cranial radiotherapy causes hypothalamus/hypophysis axis dysfunction, which is associated with an increased android/ginoide fat ratio and consequential central fat accumulation, which is responsible for releasing inflammatory molecules. High dose cranial radiation (>30 Gy to the hypothalamic-pituitary axis) determines leptin resistance on hypothalamic receptors and its increased circulation levels [17]. Leptin is an adipokine produced by adipocytes and its receptors are predominantly expressed in hypothalamic nuclei and the arcuate nucleus. After radiotherapy, this structure can be damaged with the onset of leptin resistance and leptin overproduction by fat tissue [18]. The lack of leptin action on the hypothalamus causes an increase in adipose tissue, confirmed by the finding that high circulating levels of leptin are strongly associated with BMI percentiles for age, sex, and visceral adiposity. The high level of leptin leads to glucose intolerance and insulin resistance [19]. As a consequence of leptin resistance, CCS exposed to cranial irradiation have a higher BMI, fat mass, and central adiposity. Moreover, CCS exposed to cranial radiation develop growth hormone (GH) deficiency, which is associated with elevated fasting insulin, abdominal obesity, and dyslipidemia, independent of radiation dose [20]. There is no significant difference in BMI and trunk fat between patients who received 0–20 Gy and those who received >20 Gy cranial irradiation [21]. In addition, GH substitution in patients with radiation-induced deficiency and a dysregulated hypothalamic-pituitary axis worsens insulin resistance. GH substitution leads to elevated circadian GH levels, enhancing lipid oxidation and free fatty acid production [22]. In CCS of leukemia, it is also demonstrated that the risk of hyperglycemia and insulin resistance is correlated with cranial radiation, which persists after correcting the data for BMI [23].

Radiotherapy causes an increase in the incidence of MetS in CCS even when it is performed in other parts of the body. CCS who received abdomen or chest radiation and steroid therapy have higher central systolic and diastolic blood pressure [24]. The pathogenesis is probably associated with direct vascular injury and fibrosis. In one study, patients exposed to radiotherapy but not to cardiotoxic chemotherapy had decreased left ventricle wall thickness and wall mass similar to those who received anthracyclines [25]. This mechanism was confirmed by a report that demonstrates the strong association between abdomen and liver radiation (>15 Gy) and portal hypertension in CCS of Wilms Tumor [26]. Patients exposed to abdomen radiation have the highest risk of developing type 2 diabetes and insulin intolerance as a result of adipose damage after radiation, which causes cytokine release and chronic low-grade inflammation. The exact mechanism of irradiation-induced damage is associated with mitochondrial injury-inducing hyperlipidemia and fat storage dysfunction [27]. Moreover, in patients with lymphoma treated with abdominal irradiation, the pathogenesis of diabetes is related to radiation damage in survivors that received >10 Gy to the tail of the pancreas, resulting in pancreatic insufficiency [28].

2.2. Steroid Therapy

Steroid therapy is implicated in the pathogenesis of MetS as it causes a higher risk of developing type 2 diabetes mellitus and glucose intolerance with significant central fat accumulation, cytokine release and chronic inflammation. Chronic inflammation is responsible for activating ROS and reactive nitrogen species (RNS), causing DNA damage. This process leads to vital organ failure with specific consequences: liver steatosis; premature atherosclerosis, thrombosis and myocardial infarction; osteoporosis and osteopenia; neurocognitive alteration and neuronal tissue damage [29].

Prolonged steroid-induced hyperglycemia associated with a sedentary lifestyle and irregular food intake causes permanent diabetes in CCS. The pathophysiology involves different mechanisms: increased insulin resistance, increased gluconeogenesis, and decreased insulin production. Insulin resistance is caused by increasing hepatic gluconeogenesis by activating genes coding for phosphoenol-pyruvate carboxykinase and glucose-6-phosphatase [30]. Corticosteroids also increase the transport of metabolites across the mitochondrial membranes, facilitating gluconeogenesis. Moreover, it inhibits peripheral use of glucose, leading to lipid accumulation in skeletal muscles and increasing free fatty acid delivery. This mechanism is associated with corticosteroid inhibition of GLUT4 translocation to the cell surface in response to insulin production [31]. Free fatty acids enhance the inhibition of insulin-dependent glucose uptake by peripherical tissues. In the liver, the presence of free fatty acids leads to the production of glucose, triglycerides and apoB, which are atherogenic. In particular, serum apoB is a strong predictor of cardiovascular risk [32]. Production and secretion of insulin from pancreatic beta cells is influenced by dose, time of exposure, and administration of corticosteroid treatment. Intravenous infusion or oral administration at high doses leads to acute inhibition of insulin secretion. Moreover, blood glucose variability during the day also depends on the type of corticosteroid formulation [33].

2.3. Chemotherapy

Chemotherapy drugs are involved in the genesis of MetS in CCS by their direct and indirect actions. It is not easy to understand the mechanism through which single chemotherapeutic agents act in determining MetS, as they are frequently administered together. However, it is known how some chemotherapeutic agents cause damage to the cardiovascular system. For example, anthracyclines cause cardiovascular damage and hypertension due to anthracycline-related cardiotoxicity, which causes left ventricular pathological remodeling, fibrosis, and afterload abnormalities [34]. Pathophysiology of doxorubicin-induced cardiomyocyte atrophy and death is related to p53 expression. Doxorubicin induces p53 which is necessary for the inactivation of the mammalian target of rapamycin (mTOR), which in turn is essential for protein synthesis. This leads to myocyte atrophy and reduction in heart weight [35].

CCS treated with platinum and steroids were strongly at risk of developing insulin resistance and cardiovascular risk [28,36]. The pathogenesis is associated with the direct exposure of endothelial cells to platinum, which leads to endothelial cell release of IL-1, IL-6, IL-8 and GM-CSF. Moreover, IL-1 is able to induce superoxide dismutase (SOD) from mitochondria which catalyze the conversion of O2 to H2O2, with consequent endothelial damage [37,38].

Patients affected by Acute Lymphoblastic Leukemia (ALL) receive L-asparaginase during induction therapy associated with corticosteroids. L-asparaginase can directly inhibit insulin biosynthesis, causing impaired intracellular signaling, reducing and modifying insulin receptors, and indirectly reducing insulin production via induction of pancreatitis and beta cells destruction. These mechanisms lead to a systemic insulinopenic state and hyperglucagonemia, enhanced by beta cells cytotoxicity and inflammation [39,40]. Some additional risk factors such as age and genetic conditions (e.g., Down Syndrome) can enhance prednisone-asparaginase induced hyperglycemia in ALL patients. For example, studies demonstrate that ALL patients older than 10 years of age have the highest risk of

developing MetS. The pathogenesis is probably related to sex hormone excretion during puberty that can enhance glucose intolerance and insulin resistance [41].

Moreover, all chemotherapy drugs activate inflammatory processes with the accumulation of senescent cells and the increasing of reactive oxygen species facilitates the onset of MetS [27,42]. Chemotherapy causes mucositis that alters normal intestinal flora, disturbs the microbiome, and causes febrile neutropenia with the consequent need to receive broad-spectrum antibiotics [43]. The gut environment can interact with the host through the presentation of various ligands that activate catalytic pathways for the metabolism of complex carbohydrates that produce short-chain fatty acids, anti-inflammatory and anti-proliferative lipids. These molecules modulate immune homeostasis in the gastrointestinal tract and mucous surfaces. Antibiotic- and chemotherapy-induced alterations in the gut microbiome contribute to anti-inflammatory dysfunction and increased cytokine production [44]. This mechanism influences the appearance of MetS.

3. Biomarkers Predictive of Metabolic Syndrome and Cardiovascular Disease in CCS

The definition of MetS includes biomarkers such as an increase in triglycerides, a reduction in HDL, and impaired glucose, which is defined as a fasting blood glucose of $\geq$100 and <126 mg/dL, or blood glucose $\geq$140 and <200 mg/dL at the 2 h mark of the oral glucose tolerance test [45]. 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.

Based on the pathogenetic mechanisms that lead to the onset of MetS and consequent increase in cardiovascular risk, in recent years, biomarkers capable of predicting the onset of Mets were identified in CCS [19]. Among these are the adipokines adiponectin and leptin, uric acid, the inflammatory markers high sensitivity C-reactive protein (hsCRP), Tumor Necrosis Factor-alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6), and the lipid markers apolipoprotein B (apoB) and lipoprotein(a) (Lp(a)) [19].

The mechanisms that lead to an increase/reduction in these biomarkers, the laboratory systems with which to carry out the measurements, and the reference values are analyzed below and summarized in Figure 2 and Table 1.

3.1. 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 [46]. 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 [47]. 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 [46]. 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 [48]. 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 [49,50]. In fact, adiponectin inversely correlates with intimal thickness [32,51] 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 [52]. It was shown that adiponectin correlates inversely with adiposity in survivors of brain tumors [32], with the antero-posterior diameter of infrarenal abdominal aorta in survivors of leukemia [51],

and with the appearance of MetS in pediatric survivors of lymphoma and allogeneic hematopoietic stem cell transplantation [23,53].

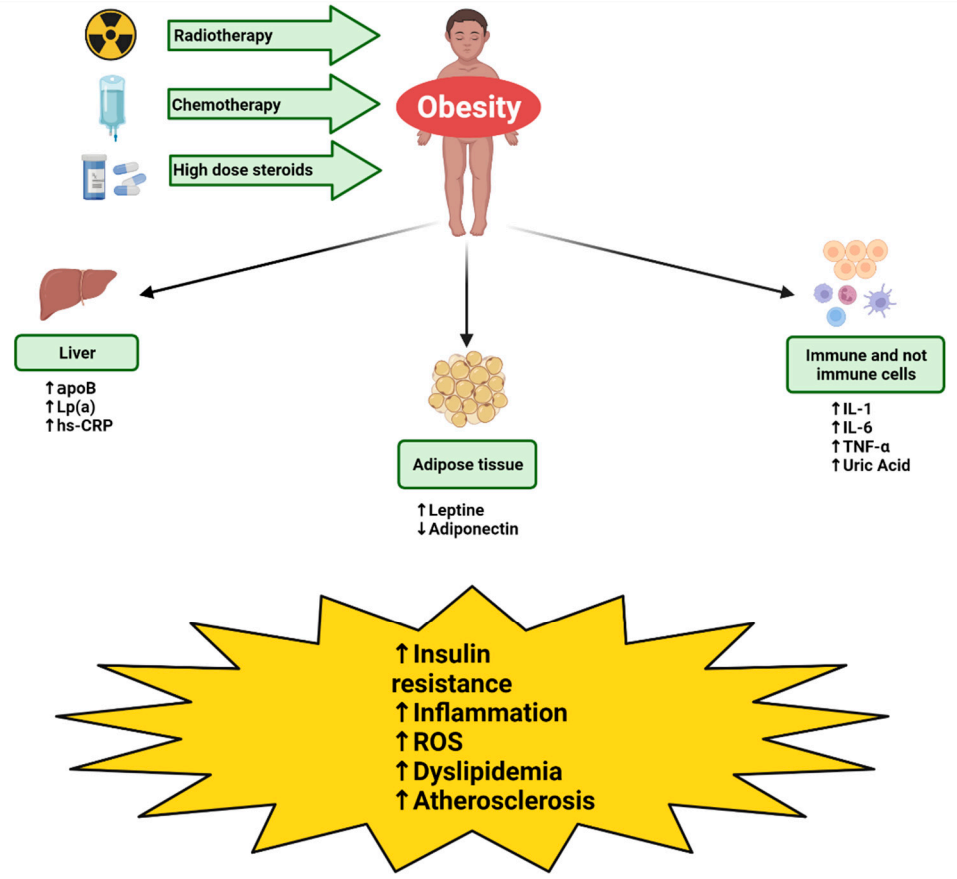

Figure 2. Mechanisms of action of the biomarkers of MetS. Radiotherapy, chemotherapy and high dose steroids cause the appearance of weight gain with a consequent increase in the hepatic production of apoB, Lp(a) and hs-CRP, a reduction in the production of adiponectin by the adipose tissue and a simultaneous reduction in the production of leptin, reduction in the production of IL-1, IL-6, TNF by the immune and non-immune cells, and uric acid. The production of these markers determines insulin resistance, inflammation, dyslipidemia, production of reactive oxygen species (ROS), and atherosclerosis.

Table 1. Biomarkers predictive of MetS. The table summarizes the structural characteristics, production sites and mechanisms of action of the biomarkers examined.

Biomarkers	Structure	Production Site	Mechanisms of Involvement in MetS	Changes in MetS
Adiponectin	Protein	Adipose tissue Cardiac and skeletal tissue	↑Insulin sensivity ↑Intracellular glucose transport ↑Oxidation of fatty acids ↓ROS and hs-CRP ↓Gluconeogenesis	Reduced
Leptin	Protein	Adipose tissue	↓Appetite	Increased (Leptin receptor resistance)
Uric Acid	Product of purine metabolism	All cells	↑ROS ↑Inflammatory cytokines ↑Insulin resistance ↑Dyslipidemia	Increased

Table 1. *Cont.*

Biomarkers	Structure	Production Site	Mechanisms of Involvement in MetS	Changes in MetS
hs-CRP	Protein	Liver cells	↑Inflammation ↑ROS	Increased
TNF-α	Cytokine	Immune and non-immune cells	↑Hepatic lipid synthesis ↑Adipose lipolisis ↑Cholesterol biosynthesis ↑Inflammation ↑Vascular insulin resistance	Increased
IL-1	Cytokine	Immune and non-immune cells	↑Inflammation ↑Insulin resistance	Increased
IL-6	Cytokine	Immune cells Osteoblasts Muscle cells	↑Inflammation ↑Insulin resistance ↑Plasma glucose ↑Free fatty acids	Increased
Apo B	Transporter protein	Liver cells	↑Atherosclerosis	Increased
Lp (a)	Transporter protein	Liver cells	↑Inflammation ↑Atherosclerosis ↑Vascular muscle cells proliferation ↓Fibrinolisis	Increased

↑ indicates an increase in plasma concentration; ↓ indicates a decrease in plasma concentration.

The measurement of adiponectin can be carried out using the enzyme-linked immunosorbent assay (ELISA) technique [51]; 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 [54], and Lausten-Thomsen et al. developed reference levels for total serum adiponectin in children and adolescents aged 6–18 years [55]. It is usually expressed in μg/mL.

3.2. 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 [56]. 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 [57]. It also regulates the axes of the thyroid gland, gonads, adrenocorticotropic hormone and cortisol growth hormone, and changes in cognition, emotions, memory, and the entire brain structure [58,59]. 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 [57]. The absence of leptin is the cause of a pathological condition characterized by severe obesity, hyperinsulinemia and dyslipidemia [60–62]. Leptin plasmatic value is influenced by sex and gender and is greater in females than in males in both children and adults [63]. In adults, leptin is positively correlated with fasting insulin concentrations [64] and is a predictor of glucose intolerance, insulin resistance and MetS regardless of underlying obesity [65]. Furthermore, elevated leptin levels were found to be a significant predictor of cardiovascular-related death and hypertension [66,67]. 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% [68]. 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 [36]. 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 [23,69]. 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 [70]. There is no strong evidence of normal pediatric leptin values [71]. 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 [72]. 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 [54]. The most frequently used unit of measurement is ng/mL.

3.3. 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 [73], and the remainder is eliminated via the substrate of hypoxanthine-guanine phosphoribosyltransferase, which recycles purines [74]. 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 [75,76]. 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 [77]. 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 [78–80]. 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 [81]. 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 [81]. 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 [82]. 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 [18]. The same evidence was also obtained in the CCS of allogeneic hemato-poietic stem cell transplantation and leukemia [53,83]. 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 [84]. In healthy adults, uric acid must be less than 6.6 mg/dL or 360 µmol/L [85]. Uric acid values are lower in pediatric patients and should be compared with age- and gender-adjusted percentiles [86]. It is usually expressed in mg/dL or µmol/L.

3.4. 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 [87]. 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 [88,89]. 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. [87]. Insulin resistance, atherosclerosis, and cardiovascular disease are associated with chronic low levels of systemic inflammation and hs-CRP levels in adults and children [90]. 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 [42,91]. This chronic low-grade inflammation facilitates the onset of MetS in CCS and the general population [92,93]. 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 [19,94,95]. 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 [96,97].

3.5. 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 [98]. 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 [99]. 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 [100] 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 [101]. In addition, TNF-α promotes hypertension, inducing vascular insulin resistance, reducing vasodilation, increasing intravascular fluid and vasoconstriction, and promoting sympathetic overactivity [102]. 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 [43]. 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 [19]. 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 [103]. It is usually expressed in pg/mL.

3.6. 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 [104–106]. There are two different isoforms of IL-1, IL-1α and IL-1β, which perform

the same biological functions [107]. IL-1α and IL-1β are produced in a wide variety of cells, especially in macrophages in lymphoid organs. In non-lymphoid organs, IL-1α and IL-1β 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 [108,109]. 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 [110,111], and IL-1α and IL-1β gene polymorphisms were reported to be associated with central obesity and MetS [112]. Furthermore IL-1, in particular IL-1β, was observed to have an insulin resistance action; as identified by Spranger et al. in a group of 27,500 subjects, increased plasma IL-1β, as well as IL-6 levels, increased the risk of developing type 2 diabetes within a 2.3 year period [113]. Necrotic adipocytes release "warning signals" capable of activating the production of IL-1α, which recruits innate immune cells into adipose tissue. Since adipocyte death is increased in adipose tissue during obesity, IL-1α plays a pivotal role in the initiation of adipose tissue inflammation during obesity by promoting the chronic inflammation typical of MetS [114,115]. 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 [116]. In children with leukemia and a solid tumor, high concentrations of IL-1 were identified [117,118]. However, there is little evidence of the role of IL-1 in the pathogenesis of MetS in CCS [19]. 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 [119]. It is usually expressed in pg/mL.

3.7. 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 [120]. 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 [121]. 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 [122]. In addition to these functions, IL-6 plays an important role in various metabolic processes as autocrine and/or paracrine actions of adipocyte function [123] 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 [124]. 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 [125]. It is demonstrated that in adults, IL-6 plays a role in the progression and severity of many forms of cancer [126], and it correlates with poor prognosis in children with neuroblastoma and acute myeloid leukemia [127,128]. Higher IL-6 values were also found in leukemia survivors [43]; however, there is not much evidence for the role of IL-6 in the pathogenesis of MetS in CCS [19]. 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 [119]. It is usually expressed in pg/mL.

3.8. ApoB

Apolipoproteins are a group of proteins involved in transport in the various tissues of lipids, which are not soluble in plasma [129]. 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) [130]. 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 [131]. 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 [132]. 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 [133]. 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 [134], and epidemiological studies show that apoB predicts the development of type 2 diabetes as much as 3–10 years in advance of clinical onset [135].

Broberg et al. demonstrated high values of apoB in CCS subjected to a high dose of anthracycline [136], and the same observation was shown in CCS of leukemia [137].

The ELISA can measure apoB, but this technique may be expensive and time-consuming, and its accuracy may vary [138]. 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 [139,140]. Yip et al. provided reference interval values for apoB in children and adolescents [141]. It is usually expressed in mg/dL.

3.9. Lp(a)

Lp(a) is a lipoprotein similar to LDL and contains apo(a) and apoB100 in a 1:1 molar ratio [142]. 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 [143]. 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 [144]. 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 [145]. Bermudez et al. showed an association between elevated levels of Lp(a) and the onset of MetS [146]; these data were also confirmed by Paredes et al. [147]. 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 [19]. Lp(a) can be measured by immunoassay; it is usually expressed in mg/dl, but the correct measurement is in nmol/L [148]. 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 [149].

4. Effectiveness of Biomarkers in Predicting Metabolic Syndrome and Cardiovascular Disease in CCS

In a recent meta-analysis, Pluimakers et al. analyzed the diagnostic and predictive value of MetS-related biomarkers in CCS. They analyzed 175 papers relating to the general population and five studies relating to CCS. They observed that uric acid, adiponectin, hs-CRP, leptin, and apoB can be used as biomarkers in MetS screening of CCS to enhance the

early identification of those at high-risk of subsequent complications [19]. They were also able to establish the prognostic value of uric acid and hsCRP in predicting the appearance of MetS. The pooled OR for the association between hyperuricemia and MetS, adjusted for age and sex, was 2.94 (95%CI 2.08–4.15) with an unadjusted pooled OR per unit increase in uric acid of 1.086 (95% CI 1.066–1.106). For hsCRP, they defined an unadjusted pooled AUC of 0.71 (95%CI 0.67–0.74) [19].

Instead, they found no sufficient evidence to confirm the value of candidate biomarkers Lp(a), IL-1, IL-6, and TNF-alpha, although for them, some relevance was shown in the general population [19].

At the moment, no other data are available on the efficacy of biomarkers in the diagnosis of MetS in CCS and we hope future studies will deepen knowledge regarding this subject. The discovery of an early biomarker of MetS will allow identified individuals to undertake lifestyle modifications such as a heart-healthy diet and regular exercise [150].

5. Conclusions

MetS is a relevant problem for CCS and is a leading cause of early death. It is currently possible to implement therapeutic strategies and treatments that block the pathogenetic mechanisms of MetS. For this reason, the identification of early biomarkers will greatly improve the survival of CCS. Uric acid and hsCRP are already effective in predicting the occurrence of MetS, and should therefore be included in CCS surveillance protocols and performed at all follow-up evaluations.

However, sufficient data are not yet available for the other biomarkers analyzed in the article, due to the small number of studies available in the scientific literature; future studies may permit a more thorough definition of their efficacy, guaranteeing an improvement in the survival of CCS.

Author Contributions: Conceptualization, A.R. (Alberto Romano), E.D.V. and S.R.; methodology, S.T. and P.M.; validation, A.R. (Antonio Ruggiero) and S.M.; data curation, G.A. and E.D.V.; writing—original draft preparation, A.R. (Alberto Romano); writing—review and editing, S.T. and S.R.; visualization, S.M.; supervision, A.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: This work was supported by Fondazione per l'Oncologia Pediatrica.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gatta, G.; Botta, L.; Rossi, S.; Aareleid, T.; Bielska-Lasota, M.; Clavel, J.; Dimitrova, N.; Jakab, Z.; Kaatsch, P.; Lacour, B.; et al. Childhood Cancer Survival in Europe 1999–2007: Results of EUROCARE-5—A Population-Based Study. *Lancet Oncol.* **2014**, *15*, 35–47. [CrossRef]
2. Vassal, G.; Schrappe, M.; Pritchard-Jones, K.; Arnold, F.; Basset, L.; Biondi, A.; Bode, G.; Eggert, A.; Hjorth, L.; Kamerić, L.; et al. The SIOPE Strategic Plan: A European Cancer Plan for Children and Adolescents. *J. Cancer Policy* **2016**, *8*, 17–32. [CrossRef]
3. Haupt, R.; Essiaf, S.; Dellacasa, C.; Ronckers, C.M.; Caruso, S.; Sugden, E.; Zadravec Zaletel, L.; Muraca, M.; Morsellino, V.; Kienesberger, A.; et al. The "Survivorship Passport" for Childhood Cancer Survivors. *Eur. J. Cancer* **2018**, *102*, 69–81. [CrossRef]
4. Attinà, G.; Romano, A.; Maurizi, P.; D'Amuri, S.; Mastrangelo, S.; Capozza, M.A.; Triarico, S.; Ruggiero, A. Management of Oral Mucositis in Children With Malignant Solid Tumors. *Front. Oncol.* **2021**, *11*, 599243. [CrossRef] [PubMed]
5. Romano, A.; Capozza, M.A.; Mastrangelo, S.; Maurizi, P.; Triarico, S.; Rolesi, R.; Attinà, G.; Fetoni, A.R.; Ruggiero, A. Assessment and Management of Platinum-Related Ototoxicity in Children Treated for Cancer. *Cancers* **2020**, *12*, 1266. [CrossRef]
6. Ruggiero, A.; Ferrara, P.; Attinà, G.; Rizzo, D.; Riccardi, R. Renal Toxicity and Chemotherapy in Children with Cancer. *Br. J. Clin. Pharmacol.* **2017**, *83*, 2605–2614. [CrossRef]

7. Sofia, R.; Melita, V.; De Vita, A.; Ruggiero, A.; Romano, A.; Attinà, G.; Birritella, L.; Lamendola, P.; Lombardo, A.; Lanza, G.A.; et al. Cardiac Surveillance for Early Detection of Late Subclinical Cardiac Dysfunction in Childhood Cancer Survivors After Anthracycline Therapy. *Front. Oncol.* **2021**, *11*, 624057. [CrossRef]
8. Talvensaari, K.K.; Lanning, M.; Tapanainen, P.; Knip, M. Long-Term Survivors of Childhood Cancer Have an Increased Risk of Manifesting the Metabolic Syndrome. *J. Clin. Endocrinol. Metab.* **1996**, *81*, 3051–3055. [CrossRef]
9. Baker, K.S.; Chow, E.J.; Goodman, P.J.; Leisenring, W.M.; Dietz, A.C.; Perkins, J.L.; Chow, L.; Sinaiko, A.; Moran, A.; Petryk, A.; et al. Impact of Treatment Exposures on Cardiovascular Risk and Insulin Resistance in Childhood Cancer Survivors. *Cancer Epidemiol. Biomark. Prev.* **2013**, *22*, 1954–1963. [CrossRef]
10. de Haas, E.C.; Oosting, S.F.; Lefrandt, J.D.; Wolffenbuttel, B.H.; Sleijfer, D.T.; Gietema, J.A. The Metabolic Syndrome in Cancer Survivors. *Lancet Oncol.* **2010**, *11*, 193–203. [CrossRef]
11. Pluimakers, V.; van Waas, M.; Neggers, S.J.C.M.M.; Van den Heuvel-Eibrink, M. Metabolic Syndrome as Cardiovascular Risk Factor in Childhood Cancer Survivors. *Crit. Rev. Oncol. Hematol.* **2019**, *133*, 129–141. [CrossRef] [PubMed]
12. Alberti, K.G.M.M.; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Cleeman, J.I.; Donato, K.A.; Fruchart, J.-C.; James, W.P.T.; Loria, C.M.; Smith, S.C., Jr. 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. [CrossRef] [PubMed]
13. Weiss, R.; Bremer, A.A.; Lustig, R.H. What Is Metabolic Syndrome, and Why Are Children Getting It? *Ann. N. Y. Acad. Sci.* **2013**, *1281*, 123–140. [CrossRef] [PubMed]
14. Al-Hamad, D.; Raman, V. Metabolic Syndrome in Children and Adolescents. *Transl. Pediatr.* **2017**, *6*, 397–407. [CrossRef]
15. Smith, W.; Li, C.; Nottage, K.; Mulrooney, D.; Armstrong, G.; Lanctot, J.; Chemaitilly, W.; Laver, J.; Srivastava, D.; Robison, L.; et al. Lifestyle and Metabolic Syndrome in Adult Survivors of Childhood Cancer: A report from the St. Jude Lifetime Cohort Study. *Cancer* **2014**, *120*, 2742–2750. [CrossRef]
16. McCracken, E.; Monaghan, M.; Sreenivasan, S. Pathophysiology of the Metabolic Syndrome. *Clin. Dermatol.* **2018**, *36*, 14–20. [CrossRef]
17. Follin, C.; Erfurth, E.M. Long-Term Effect of Cranial Radiotherapy on Pituitary-Hypothalamus Area in Childhood Acute Lymphoblastic Leukemia Survivors. *Curr. Treat. Options Oncol.* **2016**, *17*, 50. [CrossRef]
18. 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. [CrossRef]
19. 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. [CrossRef]
20. Sklar, C.A.; Antal, Z.; Chemaitilly, W.; Cohen, L.E.; Follin, C.; Meacham, L.R.; Murad, M.H. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 2761–2784. [CrossRef]
21. Miller, T.L.; Lipsitz, S.R.; Lopez-Mitnik, G.; Hinkle, A.S.; Constine, L.S.; Adams, M.J.; French, C.; Proukou, C.; Rovitelli, A.; Lipshultz, S.E. Characteristics and Determinants of Adiposity in Pediatric Cancer Survivors. *Cancer Epidemiol. Biomark. Prev.* **2010**, *19*, 2013–2022. [CrossRef] [PubMed]
22. Jørgensen, J.O.L.; Vestergaard, E.; Gormsen, L.; Jessen, N.; Nørrelund, H.; Christiansen, J.S.; Møller, N. Metabolic Consequences of GH Deficiency. *J. Endocrinol. Investig.* **2005**, *28*, 47–51.
23. Barbosa-Cortés, L.; López-Alarcón, M.; Mejía-Aranguré, J.M.; Klünder-Klünder, M.; Del Carmen Rodríguez-Zepeda, M.; Rivera-Márquez, H.; de la Vega-Martínez, A.; Martin-Trejo, J.; Shum-Luis, J.; Solis-Labastida, K.; et al. Adipokines, Insulin Resistance, and Adiposity as a Predictors of Metabolic Syndrome in Child Survivors of Lymphoma and Acute Lymphoblastic Leukemia of a Developing Country. *BMC Cancer* **2017**, *17*, 125. [CrossRef] [PubMed]
24. Meacham, L.R.; Chow, E.J.; Ness, K.K.; Kamdar, K.Y.; Chen, Y.; Yasui, Y.; Oeffinger, K.C.; Sklar, C.A.; Robison, L.L.; Mertens, A.C. Cardiovascular Risk Factors in Adult Survivors of Pediatric Cancer—A Report from the Childhood Cancer Survivor Study. *Cancer Epidemiol. Biomark. Prev.* **2010**, *19*, 170–181. [CrossRef]
25. Lipshultz, S.E.; Franco, V.I.; Miller, T.L.; Colan, S.D.; Sallan, S.E. Cardiovascular Disease in Adult Survivors of Childhood Cancer. *Annu. Rev. Med.* **2015**, *66*, 161–176. [CrossRef]
26. Green, D.M.; Wang, M.; Krasin, M.J.; Davidoff, A.M.; Srivastava, D.; Jay, D.W.; Ness, K.K.; Shulkin, B.L.; Spunt, S.L.; Jones, D.P.; et al. Long-Term Renal Function after Treatment for Unilateral, Nonsyndromic Wilms Tumor. A Report from the St. Jude Lifetime Cohort Study. *Pediatr. Blood Cancer* **2020**, *67*, e28271. [CrossRef]
27. Rossi, F.; Di Paola, A.; Pota, E.; Argenziano, M.; Di Pinto, D.; Marrapodi, M.M.; Di Leva, C.; Di Martino, M.; Tortora, C. Biological Aspects of Inflamm-Aging in Childhood Cancer Survivors. *Cancers* **2021**, *13*, 4933. [CrossRef]
28. Friedman, D.N.; Tonorezos, E.S.; Cohen, P. Diabetes and Metabolic Syndrome in Survivors of Childhood Cancer. *Horm. Res. Paediatr.* **2019**, *91*, 118–127. [CrossRef]
29. Perez, A.; Jansen-Chaparro, S.; Saigi, I.; Bernal-Lopez, M.R.; Miñambres, I.; Gomez-Huelgas, R. Glucocorticoid-Induced Hyperglycemia. *J. Diabetes* **2014**, *6*, 9–20. [CrossRef]

30. Tosur, M.; Viau-Colindres, J.; Astudillo, M.; Redondo, M.J.; Lyons, S.K. Medication-Induced Hyperglycemia: Pediatric Perspective. *BMJ Open Diabetes Res. Care* **2020**, *8*, e000801. [CrossRef]
31. Kanai, F.; Ito, K.; Todaka, M.; Hayashi, H.; Kamohara, S.; Ishii, K.; Okada, T.; Hazeki, O.; Ui, M.; Ebina, Y. Insulin-Stimulated GLUT4 Translocation Is Relevant to the Phosphorylation of IRS-1 and the Activity of PI3 Kinase. *Biochem. Biophys. Res. Commun.* **1993**, *195*, 762–768. [CrossRef] [PubMed]
32. 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. [CrossRef] [PubMed]
33. Vegiopoulos, A.; Herzig, S. Glucocorticoids, Metabolism and Metabolic Diseases. *Mol. Cell. Endocrinol.* **2007**, *275*, 43–61. [CrossRef] [PubMed]
34. Lipshultz, S.E.; Landy, D.C.; Lopez-Mitnik, G.; Lipsitz, S.R.; Hinkle, A.S.; Constine, L.S.; French, C.A.; Rovitelli, A.M.; Proukou, C.; Adams, M.J.; et al. Cardiovascular Status of Childhood Cancer Survivors Exposed and Unexposed to Cardiotoxic Therapy. *J. Clin. Oncol.* **2012**, *30*, 1050–1057. [CrossRef] [PubMed]
35. Antoniak, S.; Phungphong, S.; Cheng, Z.; Jensen, B.C. Novel Mechanisms of Anthracycline-Induced Cardiovascular Toxicity: A Focus on Thrombosis, Cardiac Atrophy, and Programmed Cell Death. *Front. Cardiovasc. Med.* **2021**, *8*, 817977. [CrossRef] [PubMed]
36. 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. [CrossRef]
37. Feldman, D.R.; Schaffer, W.L.; Steingart, R.M. Late Cardiovascular Toxicity Following Chemotherapy for Germ Cell Tumors. *J. Natl. Compr. Cancer Netw. JNCCN* **2012**, *10*, 537–544. [CrossRef]
38. Shi, Y.; Inoue, S.; Shinozaki, R.; Fukue, K.; Kougo, T. Release of Cytokines from Human Umbilical Vein Endothelial Cells Treated with Platinum Compounds in Vitro. *Jpn. J. Cancer Res.* **1998**, *89*, 757–767. [CrossRef]
39. Aisyi, M.; Andriastuti, M.; Kurniati, N. The Effect of Combination of Steroid and L-Asparaginase on Hyperglycemia in Children with Acute Lymphoblastic Leukemia (ALL). *Asian Pac. J. Cancer Prev. APJCP* **2019**, *20*, 2619–2624. [CrossRef]
40. Pui, C.H.; Burghen, G.A.; Bowman, W.P.; Aur, R.J. Risk Factors for Hyperglycemia in Children with Leukemia Receiving L-Asparaginase and Prednisone. *J. Pediatr.* **1981**, *99*, 46–50. [CrossRef]
41. Causes of Mortality in Adults Treated for Hodgkin Lymphoma. Available online: https://www.cancertherapyadvisor.com/home/cancer-topics/lymphoma/hodgkin-lymphoma-mortality-adults-treatment-risk/ (accessed on 6 April 2022).
42. 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. [CrossRef] [PubMed]
43. 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. [CrossRef] [PubMed]
44. Durack, J.; Lynch, S.V. The Gut Microbiome: Relationships with Disease and Opportunities for Therapy. *J. Exp. Med.* **2019**, *216*, 20–40. [CrossRef] [PubMed]
45. Burns, S.F.; Lee, S.J.; Arslanian, S.A. Surrogate Lipid Markers for Small Dense Low-Density Lipoprotein Particles in Overweight Youth. *J. Pediatr.* **2012**, *161*, 991–996. [CrossRef] [PubMed]
46. Achari, A.E.; Jain, S.K. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. *Int. J. Mol. Sci.* **2017**, *18*, 1321. [CrossRef]
47. 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. [CrossRef]
48. Ramakrishnan, N.; Auger, K.; Jialal, I. Biochemistry, Adiponecti. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2021.
49. Turer, A.T.; Scherer, P.E. Adiponectin: Mechanistic Insights and Clinical Implications. *Diabetologia* **2012**, *55*, 2319–2326. [CrossRef]
50. 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. [CrossRef]
51. 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. [CrossRef]
52. 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. [CrossRef]
53. 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. [CrossRef] [PubMed]
54. 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).
55. 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. [CrossRef] [PubMed]

56. 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. [CrossRef] [PubMed]
57. Dornbush, S.; Aeddula, N.R. Physiology, Leptin. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
58. Amjad, S.; Baig, M.; Zahid, N.; Tariq, S.; Rehman, R. Association between Leptin, Obesity, Hormonal Interplay and Male Infertility. *Andrologia* **2019**, *51*, e13147. [CrossRef]
59. 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. [CrossRef]
60. 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. [CrossRef]
61. Farooqi, I.S.; O'Rahilly, S. 20 Years of Leptin: Human Disorders of Leptin Action. *J. Endocrinol.* **2014**, *223*, T63–T70. [CrossRef]
62. 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. [CrossRef]
63. Wabitsch, M.; Blum, W.F.; Muche, 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. [CrossRef]
64. 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. [CrossRef]
65. 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. [CrossRef] [PubMed]
66. 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. [CrossRef] [PubMed]
67. 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. [CrossRef]
68. 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. [CrossRef] [PubMed]
69. Annaloro, C.; Usardi, P.; Airaghi, L.; Giunta, V.; Forti, S.; Orsatti, A.; Baldini, M.; Delle Volpe, A.; Lambertenghi Deliliers, G. Prevalence of Metabolic Syndrome in Long-Term Survivors of Hematopoietic Stem Cell Transplantation. *Bone Marrow Transplant.* **2008**, *41*, 797–804. [CrossRef]
70. 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. [CrossRef]
71. 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. [CrossRef]
72. 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. [CrossRef]
73. 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. [CrossRef]
74. 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. [CrossRef]
75. Zhang, C.; Li, L.; Zhang, Y.; Zeng, C. Recent Advances in Fructose Intake and Risk of Hyperuricemia. *Biomed. Pharmacother.* **2020**, *131*, 110795. [CrossRef] [PubMed]
76. Li, L.; Zhang, Y.; Zeng, C. Update on the Epidemiology, Genetics, and Therapeutic Options of Hyperuricemia. *Am. J. Transl. Res.* **2020**, *12*, 3167–3181. [PubMed]
77. 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. [CrossRef] [PubMed]
78. 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. [CrossRef]
79. 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. [CrossRef]
80. 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. [CrossRef]

81. Kimura, Y.; Tsukui, D.; Kono, H. Uric Acid in Inflammation and the Pathogenesis of Atherosclerosis. *Int. J. Mol. Sci.* **2021**, *22*, 12394. [CrossRef]
82. King, C.; Lanaspa, 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. [CrossRef]
83. 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. [CrossRef]
84. 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 Pt@Ag Nanoflowers. *RSC Adv.* **2019**, *9*, 36578–36585. [CrossRef]
85. 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. [PubMed]
86. 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. [CrossRef] [PubMed]
87. Nehring, S.M.; Goyal, A.; Patel, B.C. C Reactive Protein. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
88. 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. [CrossRef] [PubMed]
89. 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. [CrossRef] [PubMed]
90. 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. [CrossRef] [PubMed]
91. 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. [CrossRef] [PubMed]
92. Muhic, E.; Mathiesen, S.; Nielsen, M.M.; Suominen, A.; Sørensen, K.; Ifversen, M.; Nolsöe, 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. [CrossRef]
93. 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. [CrossRef]
94. 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. [CrossRef]
95. 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. [CrossRef]
96. 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. [CrossRef] [PubMed]
97. 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. [CrossRef] [PubMed]
98. 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. [CrossRef] [PubMed]
99. Sethi, J.K.; Hotamisligil, G.S. Metabolic Messengers: Tumour Necrosis Factor. *Nat. Metab.* **2021**, *3*, 1302–1312. [CrossRef] [PubMed]
100. Mathis, D.; Shoelson, S.E. Immunometabolism: An Emerging Frontier. *Nat. Rev. Immunol.* **2011**, *11*, 81–83. [CrossRef] [PubMed]
101. 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. [CrossRef] [PubMed]
102. 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. [CrossRef] [PubMed]
103. 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. [CrossRef]
104. Kaneko, N.; Kurata, M.; Yamamoto, T.; Morikawa, S.; Masumoto, J. The Role of Interleukin-1 in General Pathology. *Inflamm. Regen.* **2019**, *39*, 12. [CrossRef]
105. 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. [CrossRef]
106. 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. [PubMed]

107. 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. [PubMed]
108. 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.
109. Dinarello, C.A. The Interleukin-1 Family: 10 Years of Discovery. *FASEB J.* **1994**, *8*, 1314–1325. [CrossRef]
110. 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-1beta Contributes to Glucotoxicity in Human Pancreatic Islets. *J. Clin. Investig.* **2002**, *110*, 851–860. [CrossRef] [PubMed]
111. 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. [CrossRef]
112. 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. [CrossRef]
113. 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. [CrossRef]
114. 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. [CrossRef]
115. 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. [CrossRef]
116. Bent, R.; Moll, L.; Grabbe, S.; Bros, M. Interleukin-1 Beta—A Friend or Foe in Malignancies? *Int. J. Mol. Sci.* **2018**, *19*, 2155. [CrossRef] [PubMed]
117. 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. [CrossRef] [PubMed]
118. 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*. [CrossRef]
119. 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. [CrossRef] [PubMed]
120. Hirano, T. IL-6 in Inflammation, Autoimmunity and Cancer. *Int. Immunol.* **2021**, *33*, 127–148. [CrossRef] [PubMed]
121. Tanaka, T.; Narazaki, M.; Kishimoto, T. IL-6 in Inflammation, Immunity, and Disease. *Cold Spring Harb. Perspect. Biol.* **2014**, *6*, a016295. [CrossRef] [PubMed]
122. Harmer, D.; Falank, C.; Reagan, M.R. Interleukin-6 Interweaves the Bone Marrow Microenvironment, Bone Loss, and Multiple Myeloma. *Front. Endocrinol.* **2018**, *9*, 788. [CrossRef]
123. 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. [CrossRef]
124. Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z. The Metabolic Syndrome. *Lancet* **2005**, *365*, 1415–1428. [CrossRef]
125. Obesity-Induced TNFα 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).
126. 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. [CrossRef]
127. 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. [CrossRef] [PubMed]
128. 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. [CrossRef] [PubMed]
129. Jialal, I.; Barton Duell, P. Diagnosis of Familial Hypercholesterolemia. *Am. J. Clin. Pathol.* **2016**, *145*, 437–439. [CrossRef] [PubMed]
130. Devaraj, S.; Semaan, J.R.; Jialal, I. Biochemistry, Apolipoprotein B. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
131. 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. [CrossRef]
132. Behbodikhah, J.; Ahmed, S.; Elyasi, A.; Kasselman, 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. [CrossRef]
133. 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. [CrossRef]

134. 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. [CrossRef]
135. 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. [CrossRef]
136. 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. [CrossRef]
137. Morel, S.; Leahy, J.; Fournier, M.; Lamarche, B.; Garofalo, C.; Grimard, G.; Poulain, F.; Delvin, E.; Laverdière, C.; Krajinovic, M.; et al. Lipid and Lipoprotein Abnormalities in Acute Lymphoblastic Leukemia Survivors. *J. Lipid Res.* **2017**, *58*, 982–993. [CrossRef]
138. 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. [CrossRef] [PubMed]
139. 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. [CrossRef] [PubMed]
140. 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. [CrossRef]
141. 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. [CrossRef] [PubMed]
142. Albers, J.J.; Kennedy, H.; Marcovina, S.M. Evidence That Lp[a] Contains One Molecule of Apo[a] and One Molecule of ApoB: Evaluation of Amino Acid Analysis Data. *J. Lipid Res.* **1996**, *37*, 192–196. [CrossRef]
143. Brown, M.S.; Goldstein, J.L. Plasma Lipoproteins: Teaching Old Dogmas New Tricks. *Nature* **1987**, *330*, 113–114. [CrossRef]
144. 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. [CrossRef]
145. 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. [CrossRef]
146. 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. [CrossRef]
147. 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. [CrossRef]
148. 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. [CrossRef] [PubMed]
149. 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. [CrossRef] [PubMed]
150. Temtanakitpaisan, Y.; Saengnipanthkul, S. Monitoring of Metabolic Syndrome and Cardiovascular Disease in Childhood Cancer Survivors. *J. Adolesc. Young Adult Oncol.* **2022**, *11*, 17–26. [CrossRef] [PubMed]