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Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine

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ABSTRACT

The global epidemic of obesity is a major public health problem today. Obesity increases the risk of many chronic diseases, such as type 2 diabetes, coronary heart disease, and certain types of cancer, and is associated with lower life expectancy. The body mass index (BMI), which is currently used to classify obesity, is only an imperfect measure of abnormal or excessive body fat accumulation. Studies have shown that waist circumference as a measure of fat distribution may improve disease prediction. More elaborate techniques such as magnetic resonance imaging are increasingly available to assess body fat distribution, but these measures are not readily available in routine clinical practice, and health-relevant cut-offs not yet been established. The measurement of biomarkers that reflect the underlying biological mechanisms for the increased disease risk may be an alternative approach to characterize the relevant obesity phenotype. The insulin/insulin-like growth factor (IGF) axis and chronic low-grade inflammation have been identified as major pathways. In addition, specific adipokines such as leptin, adiponectin and resistin have been related to obesity-associated health outcomes. This biomarker research, which is currently further developed with the application of high throughput methods, gives important insights in obesity-related disease etiology and pathophysiological pathways and may be used to better characterize obese persons at high risk of disease development and target disease-causing biomarkers in personalized prevention strategies.

Contents

Abbreviations: BIA, bioimpedance analysis; BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; EPIC, European Prospective Investigation into Cancer and Nutrition; FABP-4, fatty-acid binding protein 4; GWAS, genome-wide association studies; HOMA-IR, homeostatic model assessment of insulin resistance; IGF, insulin-like growth factor; IGFBP, IGF binding protein; IL-6, interleukin-6; LEPR, leptin receptor; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAMPT, nicotinamide phosphoribosyltransferase; PCR, polymerase chain reaction; RNA, ribonucleic acid; SNP, single nucleotide polymorphisms; TNF-α, tumor necrosis factor α; WCRF, World Cancer Research Fund; WHO, World Health Organization.

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1. Introduction

The global epidemic of obesity is on the rise in almost all countries worldwide and further increases are expected for the future [1]. Highest obesity prevalence is observed for men in Western high income countries and for women in Central Asia, the Middle East and North Africa [1]. Obesity is a risk factor for a number of chronic diseases, most notably type 2 diabetes, coronary heart disease and certain types of cancer [2,3] and is associated with lower life expectancy [4]. Thus, obesity poses one of the major public health problems of our times and has a great relevance to both the healthcare system as well as individual health. Obesity is classically defined based on body mass index (BMI), although the BMI is known to be an imperfect measure of excessive or abnormal body fat accumulation, and studies have shown that taking body fat distribution with measures such as waist circumference into account may improve disease prediction [5]. Investigations into the underlying biological processes of the association between adiposity and chronic disease have suggested several biomarkers as potential mediators. These obesity biomarkers include circulating hormones and cytokines such as adipokines, which are hormones secreted by adipose tissue, as well as markers at other biological levels such as genetic or transcriptomic markers that have been recently brought forward by newer omics technologies. Besides providing knowledge about causes and mechanisms, obesity biomarkers also have the potential to be used for an alternative or extended more precise characterization of the obesity phenotype that is relevant for disease. Ultimately, such a biomarker-guided obesity definition may be the basis for personalized prevention identifying persons at high risk of disease development for refined monitoring and intervention programs.

In this review, we first discuss the strengths and limitations of currently used anthropometric measures to diagnose obesity and summarize the epidemiological evidence regarding the association between obesity defined by classical anthropometric measures and risk of chronic diseases and mortality. Subsequently, we introduce obesity biomarkers and summarize the current evidence from epidemiological studies relating these biomarkers to chronic disease risk. Regarding "obesity biomarkers", we focus on molecular markers that (1) have been associated with obesity and (2) have been proposed to describe parts of the disease-causing biological mechanisms by describing the link between obesity and chronic disease, or the molecular processes contributing to obesity.

2. Diagnosis of Obesity

The World Health Organization (WHO) defines obesity as "a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired" [6]. Traditionally, obesity is classified based on the body mass index (BMI) calculated as weight in kilograms divided by height squared in meters. According to WHO and most current guidelines for Western populations, obesity is defined as a BMI ≥30 kg/m^2 [6,7]. This classification is based on the higher risk of mortality associated with a BMI of 30 or higher. In the same guidelines, overweight is classified as BMI 25.0 to <30 kg/m^2, normal weight ranges from a BMI of 18.5 to <25 kg/m^2 and a BMI below 18.5 kg/m^2 is considered underweight. The BMI is a simple and reasonable measure to diagnose obesity, because it correlates with fat mass and is associated with morbidity and mortality as has been shown in a vast number of epidemiological studies. However, it is also well known that the BMI has some important limitations in diagnosing obesity at the individual level. First of all, while the BMI correlates with fat mass, the measure itself cannot distinguish between fat mass and lean muscle mass. Thus, individuals with relatively little body fat such as muscular athletes may have a relatively high BMI. On the other hand, it has been shown that a substantial proportion of individuals with a BMI < 30 kg/m^2 may have excessive percentage of body fatness while being labeled as non-obese based on BMI [8]. The ability to classify individuals as obese based on the BMI also differs across different ethnic groups and by age. For instance, BMI cutoffs to define overweight and obesity have been suggested to be too high for Asian populations, resulting in an underdiagnosis of excess body fatness in these populations. Ethnicity-specific BMI cutoffs to better capture body fatness and disease risk have been proposed [9], for example for Asian populations in the Asian-Pacific guidelines [10], but they have not been mentioned in the WHO guidelines to assess obesity so far [11]. Older individuals tend to have a higher percentage of body fat at a given BMI, which is why the established BMI cut-offs may also be less accurate in older populations (≥65 years). Diagnosing obesity in childhood is complex due to the rapid development that translates into substantial BMI changes with age. Most commonly, age-related reference curves have been applied, but there is little agreement on the selection of appropriate cutoffs to diagnose childhood obesity and on the appropriate reference populations [6]. Another important drawback of the BMI as measure of obesity is that it does not reflect body fat distribution. With respect to obesity-associated metabolic consequences and disease risk, visceral fat accumulation is of particular concern. While subcutaneous adipose tissue (fat tissue beneath the skin) presents the largest fat compartment by mass and size, visceral adipose tissue (in the abdominal cavity, i.e. around and between the organs in the abdomen) is metabolically more active and secretes cytokines and hormones that exert metabolic disturbances such as insulin resistance and chronic low-grade inflammation at a higher rate [12]. Waist circumference or waist-to-hip ratio pose simple measurements to assess body fat distribution and are more strongly correlated with visceral adipose tissue than BMI [13]. According to the WHO and the National Heart, Lung and Blood institute, it is recommended that in individuals with a BMI between 25.0 and 34.9 additional measurements to define abdominal obesity are undertaken, with proposed cutoffs of 102 cm in men and 88 cm in women for waist circumference, or of 0.95 in men and 0.80 in women for waist-to-hip ratio [6,7]. However, more recently it has been shown that measurement of waist circumference is relevant also for lower BMI categories, because risk of morbidity and mortality is substantially increased in individuals with low BMI but high waist circumference [14,15].

Due to the above described limitations of classical obesity measures, studies have also incorporated different more elaborate techniques to assess body compartments, including bioimpedance analysis (BIA) instruments, dual-energy X-ray absorptiometry (DXA), computed tomography (CT) and magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) scans. They allow quantifying the volume and mass of different body compartments such as adipose tissue in the subcutaneous, visceral, and coronary (fat tissue around the heart and heart vessels) compartments, and fat-free lean compartments such as bone marrow and skeletal muscle tissue. Comparisons have highlighted that especially MRI is well-suited for a direct robust quantification of fat mass [16–19], and algorithmic advancements allow nowadays an automated segmentation of the compartments with high repeatability and reproducibility of the measurements, which are very similar compared to a manual expert segmentation [20]. While these results suggest a high potential usefulness of imaging techniques for obesity research as well as clinical use and risk stratification, such measures are much more complicated to assess compared to measuring height, weight, and waist and hip circumferences, and they need additional computerized handling. In addition, guidelines and cutoffs for what

constitutes an abnormal and harmful amount of fat mass, and if this depends again on ethnicity, age, sex, and fat-free mass have not been established yet, so that currently, they still have limited applicability in clinical practice. To date, the clinical diagnosis of obesity is widely restricted to the measurement of BMI and even the simple measurement of waist circumference is rarely performed in clinical medicine.

3. Obesity Defined by Classical Anthropometric Markers and Risk of Major Chronic Diseases and Mortality

General obesity as defined by BMI as well as abdominal obesity have been related to a number of chronic diseases including but not limited to type 2 diabetes, coronary heart disease, stroke, hypertension and certain types of cancer in a huge number of epidemiological studies. Today, there is condensed information available from both study-level as well as individual-level meta-analyses from consortia of prospective cohort studies, which are useful to judge the overall available evidence. Scientific societies such as the American Heart Association, the World Cancer Research Fund and the International Agency for Research on Cancer base their judgements on systematic reviews and meta-analyses (published or self-conducted) but also use other criteria such as consistency and biological plausibility to come to a conclusion regarding causality of disease risk factors such as obesity. For a further judgment of causality, Mendelian Randomization studies on the association of obesity and health outcomes, which are now increasingly available, are useful. Findings of observational studies cannot necessarily be assumed to reflect causal associations, because they may be influenced by imperfect adjustment for confounding e.g. by socioeconomic status (residual confounding) and even in prospective studies obesity measures may have been influenced by pre-existing, yet undiagnosed disease (reverse causation). The basic idea of Mendelian Randomization is that if a risk factor plays a causal role in disease development, genetic variation leading to lifelong differences in that risk factor, e.g. genetic variation associated with a higher BMI, should also be associated with disease risk. The advantage of Mendelian Randomization is that under the assumption of the random assortment of alleles at conception, genetic variants can be used as unbiased proxy variables because they are usually unrelated to confounding factors and cannot be altered by disease occurrence [21]. Thus, Mendelian Randomization studies using genetic variants as proxy variables for lifelong exposure may circumvent residual confounding and reverse causation bias and thereby improve causal inference. Because most known genetic variants are only moderately associated with BMI, multiple single nucleotide polymorphisms (SNPs) are used for Mendelian Randomization in order to estimate the association between genetically determined higher BMI and disease risk.

In a pooled analysis of 123 cohorts from North America, Western Europe and the Asian-Pacific region providing data on 1.4 million individuals and 52,000 cardiovascular disease events, consistent positive associations between higher baseline BMI and various cardiovascular diseases including ischemic heart disease, stroke, hypertensive heart disease and diabetes were observed [22]. In the Emerging Risk Factors collaboration separate and combined associations of BMI and abdominal obesity with 14,297 fatal or first-onset non-fatal outcomes of cardiovascular disease (coronary heart disease and cerebrovascular disease) were analyzed in 58 prospective cohort studies including data from 221,934 participants (90% of European descent) [23]. BMI, waist circumference and waist-to-hip ratio each had a similarly strong association with cardiovascular disease risk, which persisted after excluding current smokers and participants of non-European descent. The shape of association was nearly log-linear with the exception of low BMI values. Positive associations for waist circumference and waist-to-hip ratio were similar at different BMI values and slightly reduced after adjustment for BMI. In this analysis, adding BMI, waist circumference or waist-to-hip ratio individually or in combination to risk prediction scores for cardiovascular disease that include information on blood pressure, history of diabetes and blood cholesterol measures, did not improve risk prediction. This finding, however, does not diminish the important role of obesity as modifiable cardiovascular disease risk factor. In contrast, because obesity is strongly associated with intermediate cardiovascular risk factors such as hypertension, diabetes and abnormal blood lipids, preventing or controlling obesity should be the number one target for prevention of cardiovascular disease before consideration of medical treatment of intermediate risk factors. Support for a causal role of obesity in cardiometabolic diseases comes from a recent Mendelian Randomization study in the UK Biobank [24]. A polygenic score of 93 single nucleotide polymorphisms explained 2% of the interindividual variation in BMI and the obtained genetically determined higher BMI was associated with significantly higher risk of hypertension, type 2 diabetes and coronary heart disease, supporting a causal role of BMI in the development of these diseases, but no causal role of BMI was found for stroke. A causal association for central adiposity (waist-to-hip ratio adjusted for BMI) based on 97 SNPs for BMI and 49 SNPs for waist-to-hip-ratio on risk of coronary heart disease, stroke and type 2 diabetes was observed in a large Mendelian Randomization study [25].

In the past 20 years, evidence accumulated that obesity is also a risk factor for certain types of cancer [3]. The current report of the World Cancer Research Fund (WCRF) concludes that there is strong evidence that being overweight or obese is associated with increased risk of 12 types of cancer: colorectal cancer, postmenopausal breast cancer, oesophageal adenocarcinoma, endometrial cancer, ovarian cancer, kidney cancer, pancreatic cancer, stomach cancer, liver cancer, gallbladder cancer, cancers of the mouth, pharynx or larynx as well as advanced prostate cancer [26]. In a meta-analysis of 7 prospective studies of older adults from the CHANCES consortium, BMI, waist circumference and waist-to-hip-ratio showed comparable positive associations with obesity-related cancers combined and with colorectal cancer [27]. Abdominal obesity as assessed by waist circumference or waist-to-hip ratio has been shown to be associated with higher risk of colorectal cancer [28] and oesophageal adenocarcinoma [29] beyond general obesity assessed by BMI. Large Mendelian Randomization studies have provided support for a causal role of BMI in the development of colorectal [30,31], pancreatic [32] and endometrial [33] cancer, while a Mendelian Randomization study on prostate cancer risk found little evidence for a causal association [34].

As the ultimate health outcome, numerous epidemiological studies have investigated the association between obesity and mortality. Relating BMI to mortality, epidemiologic studies observed different shapes of association, including J-shaped, U-shaped and linear associations. In the Prospective Studies Collaboration, BMI in relation to overall and cause-specific mortality was investigated using individual-level data from 57 prospective studies comprising 900,000 participants [4]. After excluding the first 5 years of follow-up to limit reverse causation due to effects of pre-existing disease on baseline BMI and after adjustment for smoking, lowest mortality was observed at BMI values between 22.5 and 25 kg/m^2, and above this range, each 5 kg/m^2 increment in BMI was associated with about 30% higher all-cause mortality (40% higher vascular, 120% higher diabetes, 80% higher kidney and 10% higher neoplastic mortality). Inverse associations with mortality were observed in the lower BMI range of 15–25 kg/m^2, which were attenuated when the analysis was restricted to lifelong non-smokers. Data on abdominal obesity measures were not available in the Prospective Studies Collaboration. In the European Prospective Investigation into Cancer and Nutrition (EPIC), a multicenter cohort study comprising 520,000 study participants both general obesity measured by BMI and abdominal obesity measured by waist circumference or waist-to-hip ratio were investigated [15]. For the association of BMI with mortality, higher risks were observed in the lower and upper BMI ranges than in the middle ranges. However, when adjusted for BMI, abdominal obesity showed a linear association with mortality risk. Thus, these findings suggest that assessing the fat distribution is important to predict mortality, not only at high BMI ranges but also among persons considered normal-weight based on their BMI.

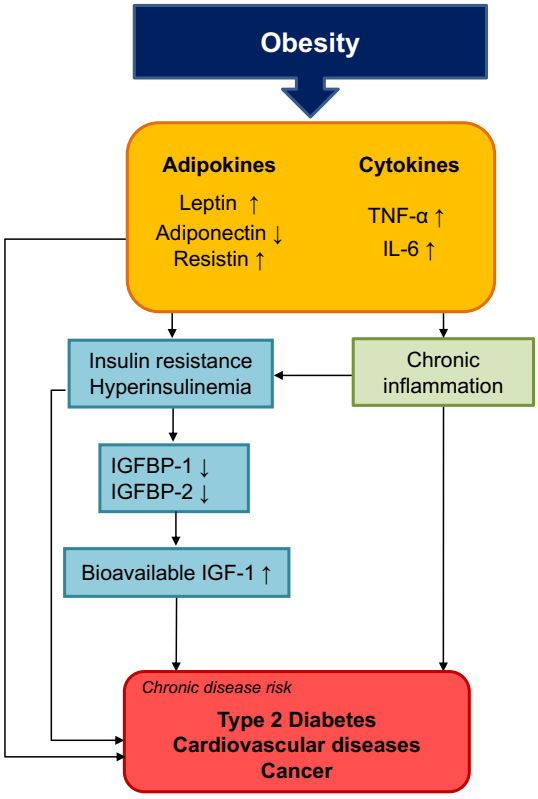

Fig. 1. Major pathways suggested to link obesity with chronic disease risk.

4. Obesity Biomarkers

While there is strong evidence from epidemiological studies on the detrimental effects of obesity defined by classical anthropometric measures on health outcomes, the underlying biological mechanisms are less understood. The endocrine function of adipose tissue, in particular visceral adipose tissue, and the hereby secreted various cytokines and adipokines have been proposed as a biological link between obesity and chronic diseases. The measurement of obesity-related biomarkers in epidemiological studies relating obesity to chronic disease risk may give important insights in the obesity-related disease etiology and pathophysiologic pathways. Resulting knowledge may be used for an extended definition of obesity beyond anthropometric measurements, i.e. to define an obesity phenotype prone to disease development based on disease-causing biomarkers. However, the current knowledge on the specific role of obesity-related biomarkers in disease development is limited and therefore, measurement of obesity biomarkers is currently not performed in the context of obesity diagnosis in clinical medicine. In the past 15 years, a growing number of epidemiological studies have investigated the association between obesity-related biomarkers and disease risk. The major pathways that have been suggested to provide a link between obesity and disease risk are the insulin/insulin-like growth factor (IGF) axis and chronic low-grade inflammation (Fig. 1). Specific adipokines such as leptin, adiponectin and others have also been investigated, which may act through one of the major pathways, but for some also distinct mechanisms to influence disease risk have been suggested. In the following, we will introduce the most well-studied biomarkers of obesity and give an overview on the current evidence from epidemiological studies relating these biomarkers to disease risk. Because in case-control studies where blood samples in cases were collected after diagnosis the biomarker under study may be influenced by the existing disease (reverse causation), we here focus on prospective studies relating pre-diagnostic levels of biomarkers to disease, most commonly in a case-cohort or nested case-control design in prospective cohort studies. In order to move from association to causality, we will also report evidence from Mendelian Randomization studies where available (Table 1).

4.1. Insulin/IGF Axis

It has been known for more than three decades that obesity is associated with impaired insulin-mediated glucose uptake, i.e. insulin resistance [35]. In the long-term, insulin resistance is associated with hyperinsulinemia, which is thought to be due to a compensation of elevated blood glucose concentrations by higher secretion of insulin from pancreatic beta cells [36]. More recently, a different chain of events has been suggested, whereby obesity first induces hyperinsulinemia followed by insulin resistance elicited by downstream pathways [37]. Insulin resistance and hyperinsulinemia have been suggested as a possible link between obesity and chronic diseases such as cardiovascular disease and diabetes [35,38]. Insulin metabolism is tightly linked with the IGF system, an evolutionary conserved group of factors exerting long-term effects on growth [39]. IGF-1 regulates cell proliferation, differentiation, migration and survival not only in healthy cells, but also in cells with genetic damage, which is why IGF-1 has been implicated to play a role in cancer development [40,41]. In addition, insulin has been shown to exert growth-promoting functions through suppression of apoptosis and promotion of cell proliferation, and thus itself may influence cancer risk [42,43]. Hyperinsulinemia leads to higher bioavailability of free, active IGF-1 by downregulating the synthesis of IGF binding proteins (IGFBP-1, IGFBP-2) on the one hand and by upregulating hepatic IGF-1 synthesis on the other hand. Thus, insulin and the IGF axis have been proposed as one biological mechanism linking obesity with cancer risk [44]. On the other hand, experimental studies in persons with diabetes showed that administration of IGF-1, especially in combination with IGFBP-3, reduces insulin requirements and improves glucose homeostasis [45]. Furthermore, experimental data suggest that IGF-1 reduces the atherosclerotic plaque burden through regulation of oxidative and inflammatory processes as well as cell senescence and epigenic modifications [46].

Biomarkers of the insulin and IGF axis have been investigated in relation to chronic disease risk in order to provide serologic evidence for these pathways playing an etiologic role in disease development. Different biomarkers, including fasting insulin, C-peptide, which is cleaved from proinsulin and is considered an indicator of endogenous insulin secretion with a longer half-life than insulin itself and IGF-1 as well as IGF-binding proteins have been investigated. Fasting insulin and C-peptide have been shown to positively correlate with BMI [35,47]. However, the relationship of IGF-1 with obesity is less obvious because of the above described effects of obesity on IGF-1 synthesis on the one hand and IGF-1 bioavailability on the other hand. Studies relating total IGF-1 to obesity found non-linear or inverse associations [48–51] with BMI. Few studies investigated obesity or BMI as determinant of free IGF-1, but a small cross-sectional study showed that free IGF-1 but not total IGF-1 was higher in obese than in normal-weight individuals [52]. In a meta-analysis of prospective cohort studies, higher fasting insulin concentrations were associated with higher risk of hypertension and coronary heart disease but not with stroke [53]. C-peptide has been shown to predict total and cardiovascular mortality in non-diabetic individuals better than other measures of insulin resistance including fasting insulin, blood glucose and the homeostatic model assessment of insulin resistance (HOMA-IR index) [54,55]. In terms of cancer, an etiologic role of the insulin/IGF-1 pathway has been proposed for colorectal cancer and other obesity-associated types of cancer such as pancreatic cancer, renal cell carcinoma, esophageal adenocarcinoma, postmenopausal breast cancer and endometrial cancer. Plausible evidence that insulin metabolism plays a role in carcinogenesis comes from the observation that the risk of developing certain types of cancer

Table 1
Overview of obesity biomarkers, their association with chronic disease/mortality and use in clinical medicine.

Type	Subtype	Biomarker	Association with chronic disease/mortality confirmed by meta-analysis	Association with chronic disease/mortality confirmed by Mendelian randomization	Use/potential use in clinical medicine
Anthropometric markers		BMI	Cardiovascular disease [22] Cancer [26] Mortality (all-cause, cardiovascular, diabetes, neoplastic) [4]	Cardiovascular disease [24] Colorectal [30,31], pancreatic [32], endometrial [33] cancer	Standard practice for obesity diagnosis (BMI > 30 kg/m^2)
		Waist	Cardiovascular disease [23] Cancer [27]		Recommended by WHO (for BMI 25.0–34.9 kg/m^2) for diagnosis of abdominal obesity (waist >102 cm in men and >88 cm in women), but not standard practice
		Waist-Hip-Ratio	Cardiovascular disease [23] Cancer [27]	Cardiovascular disease, type 2 diabetes [25]	Recommended by WHO (for BMI 25.0–34.9 kg/m^2) for diagnosis of abdominal obesity (waist-hip ratio >0.95 in men and >0.80 in women), but not standard practice
Circulating biomarkers	Insulin/IGF axis	Insulin/C-peptide	Cardiovascular disease (hypertension, coronary heart disease but not stroke) [53] Cancer [60]		Potential use for extended, biomarker-guided obesity definition
		IGF-1	Colorectal cancer [61] Cancer and cardiovascular mortality [68]		Potential use for extended, biomarker-guided obesity definition
		CRP	Cardiovascular disease, vascular and non-vascular mortality, death from several cancers [72] Colorectal cancer [79]	Colorectal cancer [81,82] Not confirmed for coronary heart disease [73]	Potential use for extended, biomarker-guided obesity definition
	Adipokines	Adiponectin	Not confirmed for cardiovascular disease [90]	Not confirmed for colorectal cancer [96]	Limited potential use based on current evidence
		Leptin	Not confirmed for cardiovascular disease [102] Colorectal cancer [104]		Limited potential use based on current evidence
		Resistin	Higher all-cause and cardiovascular mortality among patients with cardiovascular disease or diabetes [108]	Higher all-cause mortality in diabetics [109]	Potential use for extended, biomarker-guided obesity definition
		Omentin			Limited potential use based on current evidence
		Lipocalin-2			Limited potential use based on current evidence
		Chemerin			Limited potential use based on current evidence
		Visfatin			Limited potential use based on current evidence

(pancreas, endometrium, colorectum, breast) is higher in diabetics than in non-diabetics [56]. It has been hypothesized that hyperinsulinemia is specifically associated with pancreatic cancer, because the pancreas as the location of insulin synthesis is immediately exposed. Indeed, there is evidence for a positive association between pre-diagnostic insulin levels and pancreatic cancer risk [57,58]. Serologic studies relating fasting insulin or C-peptide to risk of colorectal cancer have observed positive associations [59,60]. Furthermore, a moderate positive association between IGF-1 concentrations and risk of colorectal cancer has been observed in a meta-analysis of 11 prospective studies, although in the largest investigation in EPIC, no association was reported [61]. Pre-diagnostic IGF-1 concentrations have also been related to moderately higher risk of breast and prostate cancer [62–64], while there is less evidence for other obesity-associated types of cancer. There is some evidence for a role of IGF-1 in diabetes risk from prospective studies: One small study observed a lower risk of glucose intolerance or type 2 diabetes in individuals with high versus low IGF-1 concentrations [65], while inverse associations with free IGF-1 [66] or the IGF-1/IGFBP-3 ratio as a proxy for free IGF-1 [67] but not with total IGF-1 were observed in two other studies. In a meta-analysis of prospective studies investigating IGF-1 and mortality, a U-shaped association with higher mortality risks at low and high IGF-1 concentrations was observed [68]. Interestingly, both cancer and cardiovascular mortality showed similar U-shaped associations.

4.2. Biomarkers of Inflammation

Obesity is associated with chronic low-grade systemic inflammation, which has been suggested to play a key role in the pathogenesis of insulin resistance [69]. In adipose tissue of people with obesity, the release of cytokines such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) is upregulated, which stimulates the hepatic secretion of acute-phase proteins such as C-reactive protein (CRP) [70]. In addition, obesity-induced inflammation is mediated by the secretion of pro-inflammatory adipokines such as leptin and resistin and a reduced production of the anti-inflammatory adiponectin. Due to the availability of standardized assays and its temporal stability [71], CRP is the most-studied inflammatory biomarker in relation to disease risk. However, in order to determine chronic low-grade inflammation, high-sensitivity assays that are able to determine the concentration of CRP in subclinical ranges, i.e. <10 mg/l are necessary. In some older studies, simple assays with a detection limit >10 mg/l have been used, which should be interpreted with caution. In an analysis of the Emerging Risk Factors Collaboration with individual data of 160,309 individuals from 54 prospective studies (high-sensitivity CRP assays were used in 52 of these), higher CRP concentrations have been associated with higher risk of coronary heart disease, ischaemic stroke, vascular and non-vascular mortality as well as death from several cancers [72]. However, the positive associations of CRP with coronary heart disease and

ischaemic stroke were substantially attenuated after adjustment for conventional risk factors (BMI, blood pressure, smoking, blood lipids) or other inflammatory markers. Thus, although it is known that CRP binds to LDL and is present in atherosclerotic plaques, a causal role for CRP in vascular disease has been questioned because no exact biological mechanism for CRP in atherogenesis is known. In a large Mendelian Randomization study using genetic variants in the *CRP* gene, which were unrelated to conventional risk factors and other inflammatory markers, as proxies for life-long CRP concentration, no association with risk of coronary heart disease was observed, suggesting that CRP is unlikely to play a causal role in coronary heart disease [73]. However, support for a role of inflammatory processes in the development of cardiovascular disease comes from the randomized placebo-controlled CANTOS trial, where the anti-inflammatory drug canakinumab lowered both CRP and IL-6 but did not alter blood lipids and was associated with lower risk of recurrent cardiovascular events [74]. For cancer, obesity-related chronic low-grade inflammation has been suggested to play a role in carcinogenesis through fostering cell proliferation, survival and migration [75]. There is evidence for a positive association between CRP concentrations and risk of total cancer [76,77]. Most epidemiological evidence exists for colorectal cancer [78]. In a meta-analysis of 18 prospective studies (all used high sensitivity CRP assays) higher CRP concentrations were associated with moderately higher risk of colorectal cancer [79]. Although a specific role for CRP in colorectal carcinogenesis is not known, diet-induced weight loss has been shown to reduce not only systemic inflammation but also inflammation in the colorectal mucosa [80], which may influence colorectal carcinogenesis. In a Mendelian Randomization study in EPIC, individuals carrying *CRP* genetic variants associated with lifelong higher CRP concentrations were at higher risk of colorectal cancer, supporting the hypothesis that elevated CRP is directly involved in colorectal carcinogenesis [81]. In another Mendelian Randomization study, genetically determined higher CRP was associated with higher risk of colorectal cancer but not with any other cancer [82].

4.3. Adipokines

The adipose tissue is as active endocrine organ secreting a variety of hormones, collectively named adipokines, that mediate metabolic and inflammatory consequences of obesity and may pose a link between obesity and disease risk [70]. The most abundant and most well-understood adipokines are leptin and adiponectin, whereas more recently adipokines such as resistin [83], fatty-acid binding protein 4 (FABP-4) [84], omentin [85], lipokalin-2 [86] and chemerin [87] have been proposed to play a role in the health consequences of obesity. Both, adiponectin and leptin are primarily expressed by adipose tissue. In contrast to most other adipokines, adiponectin expression is down-regulated in adipose tissue in people with obesity, resulting in the observation that individuals with obesity have lower adiponectin concentrations than individuals with normal-weight [88]. Adiponectin plays a role in energy metabolism and exerts anti-inflammatory and insulin-sensitizing effects [89]. Cardioprotective and anti-atherogenic effects of adiponectin have been suggested, but a meta-analysis of 16 prospective cohort studies did not indicate an association between circulating adiponectin and coronary heart disease or stroke [90]. Furthermore, a Mendelian Randomization study did not support the hypothesis that adiponectin plays a causal role in the pathogenesis of coronary heart disease [91]. A protective role of adiponectin in cancer development, particularly colorectal cancer, has been suggested either directly through adiponectin-mediated inhibition of cell growth and induction of apoptosis, or indirectly through favorable action of adiponectin on insulin sensitivity and reduced inflammation [92]. Circulating adiponectin concentrations have been related to lower risk of colorectal cancer [93–95], but a recent Mendelian Randomization study did not suggest a causal association [96]. Leptin is an adipokine that reflects adipose tissue mass, i.e. higher leptin concentrations are observed in obese than in normal-weight individuals [97], which suggests a state of leptin-resistance in obesity [98]. The main function of leptin is the long-term regulation of appetite and energy-balance [99], which may be impaired in leptin-resistance, resulting in obesity. Leptin has been suggested to mediate obesity-associated higher risk of cardiovascular diseases because it is considered a pro-inflammatory adipokine [70] that correlates with cardiovascular risk factors such as hypertension [100]. In addition, cancer-promoting actions of leptin have been described such as enhanced cell-proliferation, reduced apoptosis as well as promotion of migration and angiogenesis [101]. Evidence for an association between circulating leptin and cardiovascular diseases is inconclusive as shown in the most recent meta-analysis of 13 epidemiological studies of which 11 were prospective studies (nested case-control studies), where no association between higher circulating leptin and risk of coronary heart disease or stroke was observed [102]. However, a meta-analysis of 7 studies on the association between genetic variation in the leptin receptor gene (*LEPR*) and risk of cardiovascular diseases found a significant positive association for several *LEPR* genetic variants [103]. In terms of cancer, a meta-analysis of six prospective studies suggested that higher circulating leptin is associated with higher risk of colorectal cancer [104] and soluble leptin receptor has been identified as one of the main circulating biomarkers mediating the positive association between obesity and colorectal cancer risk in the EPIC study [47]. However, evidence for a causal role of leptin in the development of both cardiovascular disease and cancer remains scarce and so far no Mendelian Randomization studies have been conducted. The adipokine resistin is mainly expressed in adipose tissue in mice, whereas in humans expression in macrophages seems to play a predominant role over expression in adipocytes [105]. Resistin has pro-inflammatory properties and plays a role in obesity-associated insulin resistance, at least in mouse models [106]. Furthermore, it has been shown that resistin is involved in pathological processes leading to cardiovascular disease such as endothelial dysfunction, thrombosis, angiogenesis and smooth muscle cell dysfunction [107]. There is evidence from a meta-analysis on prospective studies mainly among patients with cardiovascular disease or diabetes that higher resistin concentrations are associated with higher all-cause and cardiovascular mortality [108]. In addition, a Mendelian Randomization study in people with diabetes showed that genetically determined higher resistin concentrations were associated with higher all-cause mortality [109]. The role of other adipokines such as omentin, lipokalin-2 and chemerin in obesity-related chronic disease risk is less-well understood, although a positive association between circulating FABP-4 and risk of diabetes [110] and heart failure [111] has been suggested in the Cardiovascular Health Study. Visfatin/extracellular nicotinamide phosphoribosyltransferase (eNAMPT) is an adipokine that was originally thought to be expressed primarily in visceral adipose tissue in obese individuals (hence the name visfatin), but more recently it has been shown that it is expressed in pre-beta cells and adipocytes in various adipose tissues (subcutaneous, visceral, epicardial fat) as well as in most cell types and in a variety of organs including heart, pancreas, liver, and skeletal muscle [112,113]. Clinical studies have suggested a role of visfatin/eNAMPT in inflammatory and atherogenic processes in various metabolic diseases including type 2 diabetes and metabolic syndrome, which is supported by mechanistic studies suggesting direct deleterious actions of visfatin/eNAMPT on the cardiovascular system. In addition, a role of visfatin/eNAMPT in cancer has been suggested [112]. However, to date prospective studies relating pre-diagnostic visfatin/eNAMPT to cardiovascular disease or cancer risk are scarce.

4.4. Omics Biomarkers

In addition to the circulating adipokines described above, the recent technological advances allow to derive further biomarkers from other biological levels. First, results from genome-wide association studies (GWAS) have categorized and replicated genetic variants with established effects on different traits. For example, the GWAS catalog

[114] currently (obtained on Sept 20, 2018 from https://www.ebi.ac.uk/gwas/) describes 2790 single nucleotide polymorphisms that have been associated with obesity. On the gene level, currently (obtained on Sept 20, 2018 from https://www.ncbi.nlm.nih.gov/gene) 1860 genes are described in their association with obesity. Some variants have been identified that cause Mendelian forms of obesity with high penetrance [115] but that are very rare on a population level. On a population level regarding common variants, the largest single meta-analysis of obesity to date has recently investigated 700,000 individuals and linked 941 near independent genetic loci to BMI [116,117]. Regarding body fat distribution, much fewer variants have been associated, a large meta-analysis including 224,459 individuals identified and replicated 49 loci [118]. New sequencing efforts can be expected to increase this list extensively with many more rare genetic variants. The strongest and most often replicated variants are located within the Fat Mass And Obesity Associated (FTO) gene [119–121]. While the mechanisms underlying the FTO genetic associations with obesity have not been fully understood, research has linked some of these genetic variants to different function of the central nervous system in the form of hunger regulation, energy expenditure, and circadian rhythm [25,27] as well as to chronic diseases including different types of cancer [122,123], but evidence is scarce and not yet convincing. Some of the other genetic variants that have been linked to obesity lie in the genes of biomarkers described in the previous section, such as in the leptin, leptin receptor, or adiponectin. As potential avenues for inclusion into personalized medicine, recent studies have investigated SNPs in the FTO and other genes regarding their relevance for post-surgery weight trajectories, and suggest some potential relevance for clinical use, however, the results still have to be replicated in larger studies [124–126].

Investigating the association of genes with obesity on the gene expression level can yield more functional information by investigating relevant tissues such as subcutaneous, visceral, coronary, and ectopic adipose tissue as well as the brain. Furthermore, as gene expression is much closer to obesity traits in terms of molecular pathways as compared to genetic variants, from a methodological perspective, often, smaller samples can yield evidence on transcriptomic associations. There exist some studies using polymerase chain reaction (PCR) to study candidate genes such as adiponectin, leptin and others in often specific populations and diseases [127–133]. However more convincing evidence from transcriptome-wide studies using RNA sequencing methods on larger samples is still in its infancy to identify novel genes as biomarkers for obesity in humans [134–136].

Further novel biomarkers can include epigenetic markers [137], markers from proteomic [138,139] and metabolomic [140] studies as well as signatures of the microbiome [141–143]. Many studies have been conducted in the field of metabolomics [140,144–146]. The results provide novel biomarkers, potential targets for interventions, and hints for underlying biological mechanisms and pathways in obesity. In the field of metabolomics, alterations in many metabolites have been found to be associated with obesity [147]. Not unexpectedly, many of these metabolites are also altered in type 2 diabetes, including different amino acids (such as branched chain amino acids), lipids, carbohydrates, and nucleotides. What may be more interesting is that some of these metabolites have also been found to be altered prior to the onset of type 2 diabetes [148]. For example, in the EPIC-Potsdam study, among 163 metabolites, 14 metabolites were found to be associated with risk of developing type 2 diabetes. Serum hexose, phenylalanine, and diacyl-phosphatidylcholines C32:1, C36:1, C38:3, and C40:5 were associated with increased risk of type 2 diabetes and serum glycine, sphingomyelin C16:1, acyl-alkyl-phosphatidylcholines, C34:3, C40:6, C42:5, C44:4, and C44:5, and lysophosphatidylcholine C18:2 with decreased risk [148]. Importantly, while many of these markers are on the one hand also related to obesity, they were associated with type 2 diabetes risk independently of BMI and waist circumference, suggesting that they may improve the prediction of disease. In fact, their addition to traditional diabetes markers significantly improved the area under the receiver operator characteristics curve (ROC), indicating improved discrimination [148].

5. Conclusion

Anthropometric measurements such as BMI for general obesity and waist circumference for abdominal obesity are the predominant measures to diagnose obesity in the clinical context as well as in epidemiological research. Their strong and consistent association with health outcomes such as type 2 diabetes, coronary heart disease and certain types of cancer underlines that these are reasonable, simple instruments. For the detailed investigation on the role of body fat composition in disease etiology, however, more refined technologies such as MRI are expected to play a major role in the future obesity research. The knowledge on the underlying biologic mechanisms and pathophysiologic pathways in the association between obesity and chronic disease risk has developed substantially in the past decades with a major contribution of epidemiologic biomarker studies. The insulin/IGF axis and chronic low-grade inflammation have been identified as major pathways and specific adipokines such as adiponectin, leptin and resistin have been related to disease outcomes. With the ongoing application of high throughput methods, novel biomarkers may be identified on a gene expression, epigenetic, metabolomic or microbiome level. Since many of the biomarkers discussed here have been shown in individual studies to be related to disease risk even after taking BMI and waist circumference into account, knowledge on disease-causing obesity biomarkers holds promise to be used for a more refined diagnosis of obesity beyond anthropometric measurements to more precisely identify persons at high risk of disease development. Nevertheless their application in clinical practice currently is premature, and further studies are warranted.

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KN drafted the article. SK and TP revised the article critically for important intellectual content. All authors participated in the conception and design of the article and approved the final version to be submitted.

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