

Obesity research: Status quo and future outlooks

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Abstract

Obesity is a multifactorial disease showing a pandemic increase within the last decades in developing, and developed countries. It is associated with several severe comorbidities such as type II diabetes, hypertension, sleep apnea, non-alcoholic steatosis hepatitis and cancer. Due to the increasing number of overweight individuals worldwide, research in the field of obesity has become more vital than ever. Currently, great efforts are spent to understand this complex disease from a biological, psychological and sociological angle. Further insights of obesity research come from bariatric surgery that provides new information regarding hormonal changes during weight loss. The initiation of programs for obesity treatment, both interventional and pharmaceutical, are being pursued with the fullest intensity. Currently, bariatric surgery is the most effective therapy for weight loss and resolution of comorbidities in morbid obese patients. Reasons for weight loss and remission of comorbidities following Roux-en-Y-Gastric Bypass,

Sleeve Gastrectomy, and other bariatric procedures are therefore under intense investigation. In this review, however, we will focus on obesity treatment, highlighting new insights and future trends of gut hormone research, the relation of obesity and cancer development *via* the obesity induced chronic state of inflammation, and new potential concepts of interventional and conservative obesity treatment.

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Key words: Obesity; Cancer; Gut hormones; Bariatric surgery

Core tip: This review focuses on the latest obesity research breakthroughs, current therapy options, future outlooks, also from a view of a surgeon as well as recently identified molecules that promote obesity and its comorbidities, outlining their great potential as new target molecules in the fight against the global pandemic, called "obesity".

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INTRODUCTION

Obesity is a multifactorial disease caused by an energy sparing lifestyle on a predisposed polygenetic background. An obese person is defined as having a body mass index (BMI) greater than 30 kg/m². Within the last decades, there has been an extraordinary increase in the worldwide prevalence of obesity becoming a major human health threat especially in developing and developed countries with a tendency to rise. Being referred to as a global pandemic^[1], the number of overweight or obese

individuals increased up to 2.1 billion worldwide. Unfortunately, no single country announced decreasing numbers of obese individuals during the last three decades^[2]. Obesity is associated with several severe comorbidities (Figure 1) such as type II diabetes mellitus (T2DM), hypertension, sleep apnea, non-alcoholic steatosis hepatitis (NASH) and cancer. Obesity-related diabetes can lead to coronary heart disease, apoplex or kidney failure. Over 80% of all patients with type II diabetes in the United States are overweight and up to 20% of United States health expenditures are estimated to be spent on treating obesity-related diseases^[3].

It is expected that NASH will be the leading cause of liver transplantation within the next years^[4]. Additionally, obesity is associated with an increased risk of developing various cancer entities such as colorectal-, esophageal-, liver- and breast cancer^[5]. Visceral-, orthopedic or cardiac surgical treatment of obese patients is associated with higher complication rates^[6-9]. Subsequently, obesity is the origin of a wide spectrum of diseases and a cofounding factor hindering adequate treatment. Due to this reasons, obesity and overweight are associated with an increased risk of death. Thus, therapy for obesity should be individually tailored and various factors such as sex, obesity degree, individual health risks should be taken into account^[10,11].

Secondary causes for obesity like endocrine disorders (*e.g.*, hypothyroidism, cushing disease), drug-induced obesity (*e.g.*, glucocorticoids, psychoactive drugs), inherited syndromes (*e.g.*, Prader-Willi syndrome, Bardet-Biedl syndrome) or monogenetic disorders (leptin receptor, melanocortin receptor) play a minor role or are cofactors in causation of obesity in daily practice. Therefore, identifying single reasons for obesity is a complex task. Intervention strategies for weight loss and maintenance at the individual and community level are strongly needed to reduce general health risks as well as health expenditures.

STATUS QUO

Due to the increasing number of overweight individuals worldwide, research in the field of obesity has become more vital than ever. As a multifactorial disease, research is conducted at a wide variety of areas. Currently, great efforts are spend to understand this complex disease from a biological, psychological and sociological angle. Further insights of obesity research come from bariatric surgery, which display new information regarding the hormonal changes during weight loss. The initiation of programs aiming to treat obesity, both interventional and pharmaceutical, are being pursued with the fullest intensity. There are various scopes of possible research activities. In this review, however, we will focus on obesity treatment, highlighting new insights into gut hormones and the relation of obesity and cancer development.

Multidisciplinary Treatment Modalities-or, how to lock the stable door after the horse had bolted

Among physicians there is consensus, to treat obese patients multidisciplinary. After diagnosis, the patient

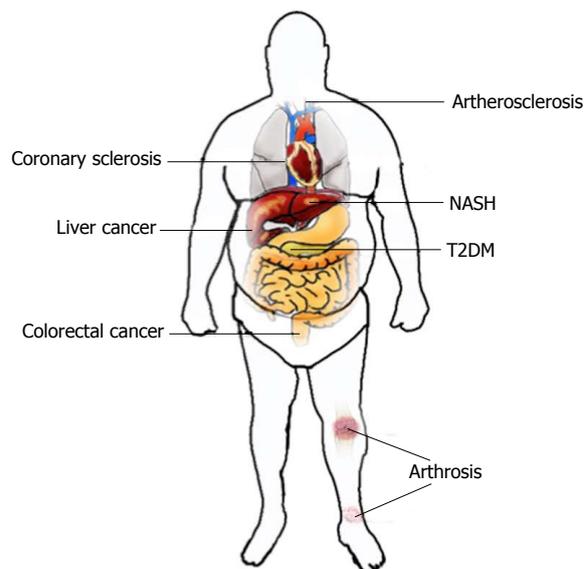


Figure 1 Obesity related diseases. T2DM: Type 2 diabetes mellitus; NASH: Non-alcoholic steatosis hepatitis.

should undergo a multimodal therapy concept based on individualized dietary education focusing on reducing energy intake, physical exercising, pharmacological therapy and psychological attendance with behavioral therapy. For the latter, many efforts to modify the behavior of obese individuals through encouragement of changes in dietary intake along with physical activity have not declined the obesity epidemic, unfortunately. The primary causes are high rates of therapy abandonment and poor patient compliance.

Patients who completed a comprehensive program including a low-calorie diet are able to lose approximately 15%-25% of their initial body weight during 3 to 6 mo of treatment. After therapy, most patients maintain a weight loss of 8% one year after treatment, 7% three years after treatment, and 5% four years after treatment^[12]. These results represent the best-case scenario, excluding patients who dropped out of their programs. It was already shown that patients who have completed structured weight loss programs, maintained their weight loss of less than 3 kg on average after 5 years; patients who accomplished more radical low-calorie diets had significantly higher weight loss of up to 20 kg and maintained more weight loss over time^[13]. In a randomized study, Jeffery *et al*^[14] evaluated the efficacy of long-term weight loss comparing one group with behavior therapy and an energy expenditure goal of 1000 kcal per week to a group of patients with high physical activity treatment and an energy expenditure goal of 2500 kcal per week. The high activity group showed significant higher weight loss and long term weight loss maintenance, reflecting that mobility is of high importance^[14].

Is bariatric surgery the best choice for long-term weight loss accompanied by remission of comorbidities in severe obese (BMI > 40 kg/m²) patients?

Bariatric surgery is more effective for weight loss and

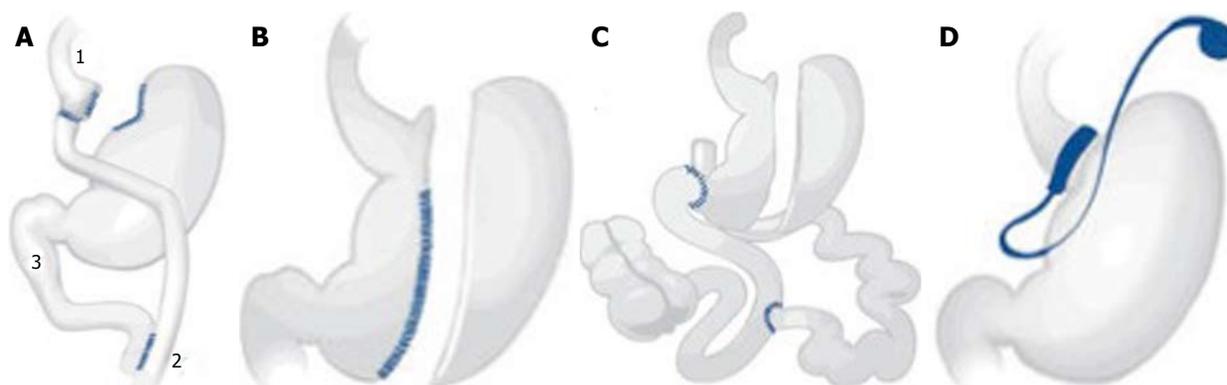


Figure 2 Bariatric surgical procedures. A: Roux-Y gastric bypass; B: Sleeve gastrectomy; C: Biliopancreatic diversion with duodenal switch; D: Gastric band.

resolution of comorbidities than conventional medical treatment modalities^[15,16]. A variety of procedures are described in the literature but only Roux-Y gastric bypass (RYGB) (46.6% of all bariatric procedures worldwide), sleeve gastrectomy (SG) (27.8%), adjustable gastric banding (GB) (17.8%) and in a smaller proportion biliopancreatic diversion with duodenal switch (BPD/DS) (2.2%) are performed in a notable quantity^[17].

Gastric bypass was first performed in the 1960s by Mason *et al.*^[18]. It was modified to a RYGB in the 1970s^[19]. It is still the most common bariatric surgical procedure. The combination of food-intake restriction by a small pouch and malabsorption through the smaller common channel (Figure 2A) leads to long-term weight loss^[15]. Also, hormonal changes after surgery may have a great impact on weight loss and diabetes remission.

SG (Figure 2B), includes the resection of the greater curve of the stomach. It is the first step of the BPD/DS (Figure 2C). BPD/DS can be performed by a two step procedure; a minority of patients do not need the second surgical step for weight loss^[20]. While SG is described as a primary restrictive procedure, including minor hormonal changes, BPD/DS causes malabsorption and leads to a higher rate of deficiencies^[21]. GB, which was developed in the 1970s, restricts food-intake by an inflatable, adjustable gastric band resulting in a small gastric pouch (Figure 2D). Since it is based on restriction only, it is the most insufficient bariatric surgical procedure regarding long-term weight loss^[22].

Overall, a preoperative multidisciplinary program is recommended. Our own clinical experiences and a review of the literature revealed that bariatric surgery for severe obese patients results in extensive weight loss and long-term comorbidity remission in a very short time frame.

There is no evidence for conventional treatment leading to sufficient excess weight loss in severe obese patients.

Padwal *et al.*^[23] performed an observational study of 500 patients with a two years follow-up. Three patient cohorts were included in which 200 patients received medical treatment, 150 patients received bariatric surgical treatment, and 200 patients received no therapy and were grouped as being waitlisted. Medically treated patients

received individualized and intensive medical management consisting of a 24-36 wk life style counseling (diet education, physical exercise, and behavioral therapy) and were observed by a multidisciplinary staff which is mandatory before bariatric surgery. Mean weight loss in the waitlisted group was 0.9%, 1.8% in the medically treated group and 22% in the surgery group. The proportion of patients who achieved at least 5% weight loss was 17% in the waitlisted group, 32% in the medically treated group and 75% in the surgery group. The prevalence of hypertension, diabetes and dyslipidemia was reduced in the surgical group, but remained unchanged or increased in the medically treated and waitlisted group^[23].

A large meta-analysis included 164 studies (37 randomized controlled trials and 127 observational studies). A total of 161756 patients were analyzed regarding effectiveness and outcome after bariatric surgery.

One year after surgery the patients showed 60% excess weight loss (EWL), and 57% EWL after 3 years. T2DM remission after surgery was 92%, hypertension remission was 75%, dyslipidemia remission was 76%, cardiovascular diseases remission was 58% and remission of sleep apnea was 96%, reflecting that surgical intervention may increase the long-term quality of life^[24].

Interestingly, 75.3% of patients that received bariatric surgery showed excess weight loss, whereas patients that had received conventional therapy showed only 11.3% excess weight loss. Moreover, remission of T2DM was reported in 63.5% of cases in surgery group, compared to 15.6% of patients in the conventional therapy group^[25]. Subsequently, there is no evidence for conventional treatment leading to sufficient EWL in obese patients with a BMI greater 40 kg/m². In fact, the only efficient treatment showing results in EWL and release of obesity associated diseases results from bariatric surgery. However, there is a strong recommendation to include the patients to a perioperative multidisciplinary medical treatment consisting of dietary changes, exercising and behavioral therapies. There is evidence that preoperative multidisciplinary preparation and education may lead to better long-term effects of bariatric surgery.

In sum, bariatric surgery is currently the only effective treatment for morbid obesity^[26]. Reasons for weight loss

Table 1 Gut hormones and their clinical relevance

Peptide	Production site	Effect	After bariatric surgery	Potential pharmaceutical intervention
Ghrelin	Stomach, mainly fundus	Appetite stimulating Growth hormone releasing	↓	Receptor antagonists GOAT inhibition Vaccination
GLP-1	L-cells of the distal small bowel	Postprandial insulin secretion Suppresses glucagon secretion Delays gastric emptying Suppresses appetite	↑	Weight loss in patients with diabetes Off-label use in obese patients
GIP	Duodenum, jejunum	Postprandial insulin secretion Energy expenditure	↓	GIP receptor antagonist
CCK	Duodenum, jejunum	Delays gastric emptying Suppresses appetite	↑	CCK analogue substance
PYY	Distal small bowel	Delays gastric emptying Suppresses appetite	↑	Long-acting analogue substance
PP	Distal small bowel	Suppresses appetite	↔	PP analogue substance
OXM	L-cells of the distal small bowel	Delays gastric emptying Suppresses appetite Increase energy expenditure	↑	Receptor agonist

Modified according to Kim *et al.*^[35]. GLP-1: Glucagon-like peptide-1; GIP: Glucose-dependent insulinotropic polypeptide; CCK: Cholecystokinin; PYY: Peptide YY; PP: Pancreatic polypeptide; OXM: Oxyntomodulin; GOAT: Ghrelin O-acyltransferase.

and remission of comorbidities following RYGB, SG, and other bariatric procedures are therefore in a strong research focus.

Gut hormones and their impact on weight loss

Alterations of gut hormone serum levels after RYGB influence appetite, satiety, energy expenditure, and glucose homeostasis^[27-29]. Several hormones and peptides are considered to be involved in weight loss in bariatric patients (Table 1).

Incretins are gut-derived peptides that increase pancreatic insulin secretion. The Glucagon-like peptide (GLP-1) and Glucose-dependent insulinotropic polypeptide (GIP) are well explored. GLP-1 and its analogues are used to treat diabetes. Beside its stimulating effects on β -cells of pancreatic Langerhans' islets, GLP-1 also suppresses glucagon secretion, delays gastric emptying and suppresses appetite^[30,31]. Therefore, GLP-1 is currently under intense discussion to become a potential therapeutic drug for obesity treatment^[32].

Ghrelin is mainly produced in the fundus of the stomach and plays an important role in satiety. When administered to humans, it increases food intake. Several studies showed that postprandial reduction of Ghrelin after bariatric surgery led to weight loss and T2DM remission^[33,34]. Therefore, lowering of Ghrelin plasma levels by non-surgical interventions might be a useful approach for obesity treatment. Different approaches already exist in the development of anti-obesity drugs. Pharmacological molecules like Ghrelin antagonists or Ghrelin receptor antagonists showed heterogeneous results in food intake reduction^[35]. Other strategies are the inhibition of Ghrelin O-acyltransferase (GOAT) that is required for activation of Ghrelin^[36] or lowering body weight by a vaccination targeting Ghrelin^[37].

Administration of Oxyntomodulin (OXM) decreases food intake and reduces body weight in rats^[38]. Further-

more, OXM has been shown to increase energy expenditure^[39]. The combination of decreasing energy intake and increasing energy consumption qualifies OXM to be a potential agent for bariatric treatment. Moreover, a plethora of other gut hormones and peptides are currently under intense investigation regarding weight loss. Interestingly, there is also evidence that various gut hormones are related to cancer growth and cancer development making their physiological understanding even more alluring^[40].

Obesity and cancer

Morbid obesity is associated with various types of cancer: Epidemiological studies identified an association of morbid obesity and several types of cancer disease, such as colorectal cancer, endometrium carcinoma, postmenopausal breast cancer, kidney cancer, esophageal cancer, pancreatic cancer, gallbladder cancer, liver cancer, and hematological malignancies^[41,42]. Obese patients have a tendency for worse prognosis and outcome after cancer treatment and an increased risk of cancer related morbidity^[43]. Calle *et al.*^[5] conducted a prospective study to examine the association of obesity and cancer related mortality. They concluded that increased body weight is associated with increased death rates for all cancers combined.

The link between obesity and cancer is still poorly understood. Several adipokines, growth factors, signaling pathways, inflammatory processes as well as the general demodulation of energy-balance and the lack of calorie restriction are being intensively discussed.

Adipokines are involved in cancer development: Traditionally, the adipose tissue was considered to be an energy storage organ. In recent years, however, it became evident that it also functions as an endocrine organ. Besides estrogen, it produces and secretes various adipokines and cytokines. Leptin and adiponectin, two well characterized adipokines, are associated with cancer development^[44].

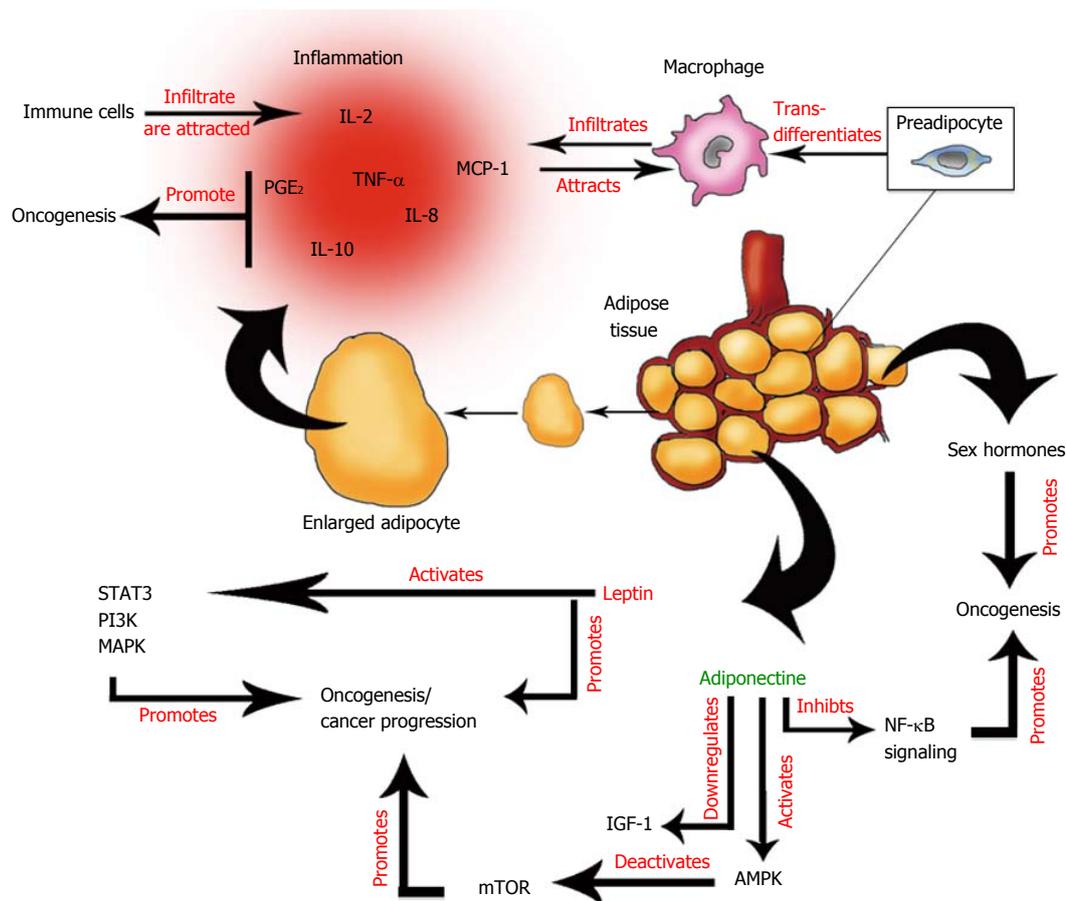


Figure 3 Endocrine, inflammatory, and cancer promoting effects of adipose tissue. IL-8: Interleukin 8; PGE₂: Prostaglandin E₂; TNF- α : Tumor necrosis factor- α ; MCP-1: Monocyte chemoattractant protein-1; STAT3: Signal transducer and activator of transcription 3; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; MAPK: Mitogen-activated protein kinase; NF- κ B: Nuclear-factor-kappa-light-chain-enhancer activated B cells; IGF-1: Insulin-growth factor-1; AMPK: 5'AMP-activated protein kinase; mTOR: Mechanistic target of rapamycin.

Leptin concentration in serum correlates positively with the patients' adipose tissue reserves and their nutritional condition. Moreover, leptin has been identified to be a potential mediator of cancer development^[45], which is able to activate various key players of different signaling cascades like phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3). More interestingly, leptin signaling promotes the progression of different cancers^[46-48].

Adiponectin is mainly secreted by visceral fat cells and acts adversary to leptin. It is inversely associated with obesity, hyperinsulinemia, and inflammation and may have anti-cancer effects by decreasing insulin-growth factor-1 (IGF-1) and mechanistic target of rapamycin (mTOR) signaling by activation of 5'AMP-activated protein kinase (AMPK). Also anti-inflammatory actions of adiponectin are described through inhibition of nuclear-factor-kappa-light-chain-enhancer activated B cells signaling (NF- κ B)^[49].

Increased carcinogenesis in obese patients might be due to chronic inflammation

Recent studies suggest a causal link of obesity related

diseases (Figure 3) and low-grade/chronic inflammation (Figure 3)^[50-52].

In humans, the immune system is of major relevance, which in turn, is able to form a defence shield against bacteria, viruses, or injured cells. A hallmark of the immune system is its most powerful weapon, the "inflammatory response" which was already noticed by a German pathologist called Rudolf Virchow in 1863. Despite the fact that humans without a functional immune system are not able to survive, too much inflammation can have a great impact and may cause serious damage to the healthy individual. Well-known chronic inflammatory diseases occur in patients that suffer from psoriasis or rheumatoid arthritis. A possible link between infections and cancer already exists, since stomach cancer may result from *Helicobacter pylori* infections or liver cancer from hepatitis (B-, C-) virus infections. A unique feature of these infections is the chronic inflammation response, which is primarily mediated by specific immune cells, such as macrophages and granulocytes that infiltrate the tumor. The latter is known to be recruited by tumor-released attractants. Once leucocytes infiltrate the tumor, they start to secrete chemokines and thereby initiate blood vessel growth/angiogenesis to allocate oxygen and nutrients,

which are relevant for tumor growth.

Circulating immune cell recruitment is a crucial feature of immune response

Macrophages: In obese individuals, macrophages infiltrate and expand in adipose tissue. Quantitative and functional changes of these cells affect adipose tissue inflammation. Exposure of macrophages to cytokines promotes two different activation states inducing to divergent polarizations. M1 macrophages are activated by tumor necrosis factor- α (TNF- α), Interferon- γ (IFN- γ), and bacterial endotoxins such as lipopolysaccharides. They are characterized by high levels of interleukin (IL)-12 and IL-23, and low levels of IL-10 as well as inflammatory cytokines^[53]. Contrarily, M2 macrophages are attracted by IL-4, IL-13, IL-10, and glucocorticoid hormones. Both types are part of innate immune response. M1 macrophages may induce chronic inflammation, whereas M2 macrophages tend to act anti-inflammatory^[54]. It has been suggested, that a phenotypic switch from M2 to M1 occurs in fat tissue^[55], however, this model is discussed controversially.

Eosinophiles: Eosinophiles levels are negatively correlated with obesity and adipose tissue in mice. Wu *et al*^[54] could show, that eosinophiles promote an M2-polarization of macrophages by secreting IL-4 and IL-13 and a down regulation of M1 macrophages in adipose tissue.

Mast cells: Mast cell levels in adipose tissue are elevated in obese animals^[56]. Mast cell ablation reduces body fat and benefits glucose homeostasis in mice. This effect is induced by IL-6 and IFN- γ . Also, pro-angiogenic factors such as Cathepsins may influence mast cell levels^[56].

Myeloid-derived suppressor cells: In adipose tissue, Myeloid-derived suppressor cells (MDSCs) have an inhibitory effect on inflammation by suppressing CD8⁺-T cells and promoting M1 to M2 macrophage switch in favour for M2 macrophages^[57]. The state of chronic inflammation in adipose tissue leads to an accumulation of MDSCs^[58]. Being part of immune autoregulation by MDSCs suppress overt inflammatory immune response in chronic inflammation^[59].

CD4⁺-T cells: CD4⁺-T cell activation is mediated by class II major histocompatibility complex (MHC II) molecules presented by macrophages and dendritic cells. When activated, CD4⁺-T cells secrete cytokines, which attract pro-inflammatory cells. Three groups of T cells can be distinguished, namely T_{H1}, T_{H2}, and T_{H17}.

The ratio of T_{H1}/T_{H2} cells is significantly enhanced in high fat diet induced obesity, since T_{H2} cells are undermined by IFN- γ producing T_{H1} cells^[60]. CD4⁺-T cell substitution in immunodeficient mice eventuates in reduction of weight gain, adipocyte cell size, and improvement of glucose homeostasis^[60]. The STAT6 pathway is essential for T_{H2} differentiation, thus STAT6 deficient CD4⁺-T cells do not show any effect of reconstitution on glucose

homeostasis and body weight gain^[60].

Regulatory T cells: CD4⁺-T cells can transdifferentiate into immunosuppressive CD4⁺CD25⁺-regulatory T cells (T_{reg})^[61]. Obesity is associated with reduced levels of T_{reg} cells in visceral adipose tissue in mice and humans^[62,63]. T_{reg} cell depletion enhances circulating insulin levels and levels of pro-inflammatory cytokines in adipose tissue of lean mice^[62]. Up regulation of T_{reg} on the other hand improves insulin sensitivity and enhances anti-inflammatory cytokine IL-10 levels^[62]. Also, T_{reg} function to suppress pro-inflammatory immune response and promote macrophage M1 to M2 switch by secreting IL-4, IL-10, and IL-13^[64].

CD8⁺-T cells: CD8⁺-T cell activation is mediated by MHC I. Activated CD8⁺-T cells induce lysis of target cells by producing various cytokines and chemokines.

Adipose tissue of obese animals^[65] and humans^[60] show a significant increase of CD8⁺-T cell levels. CD8⁺-T cells lead to elevation of macrophages in adipose tissue and promote polarization into M1 macrophages^[63]. CD8⁺-T cell deficient mice have fewer levels of macrophages in adipose tissue and less levels of TNF- α and IL-6^[63].

Natural killer T cells: When activated by lipids, natural killer T (NKT) cells produce a significant amount of T_{H1}- and T_{H2}-responsive cytokines, such as IFN- γ and IL-4^[66]. NKT cells can either promote or suppress inflammatory response by promoting either T_{H1} or T_{H2} cell activation^[67,68]. Interestingly, NKT cell levels are reduced in human omental adipose tissue^[69]. The role of NKTs in obesity still remains unclear.

B cells: After high fat diet, accumulation of B cells can be detected in adipose tissue of mice. This accumulation is associated with high levels of pro-inflammatory immunoglobulin G2c^[70]. B cells promote T cell modulation and macrophage polarization by producing pathogenic Ig-G antibodies. Ig-G, however, increases inflammatory response^[70]. The specific role of B-cells and Ig-G in inflammatory response in obesity has yet to be further investigated.

Mediators of inflammatory response: Preadipocytes can transdifferentiate into macrophages^[71]. Also they tend to enlarge due to oxygen diffusion resulting in hypoxia, inflammation and increased macrophage infiltration. Enlarged adipocytes produce a variety of inflammatory cytokines and show greater insulin resistance than normal sized ones. Levels of prostaglandin E2, TNF- α , IL-2, IL-8, IL-10, and monocyte chemoattractant protein-1 (MCP-1) are elevated in the microenvironment of enlarged adipocytes. The inflammatory environment attracts macrophages and induces production of additional pro-inflammatory mediators^[71].

NF- κ B is a central transcription factor that is activated upon bacterial and viral stimuli. It activates gene

expression associated with apoptosis, cell proliferation, inflammation, tumorigenesis, metastasis, and angiogenesis^[72]. In addition, increased NF- κ B expression and activation is associated with insulin resistance.

The frequent up-regulation of NF- κ B in many cancers is already known^[73]. The increased expression and “uncontrolled” activation of NF- κ B may induce cancerogenesis^[74,75]. Interestingly, NF- κ B gets activated upon leptin stimulation in preneoplastic and neoplastic human colonic epithelial cells *in vitro*^[76,77].

Inflammasomes, by definition cytosolic multiprotein complexes, activate IL-1 β and IL-18 during infection or tissue damage^[78]. They can be sub-divided into different inflammasome sub-groups such as nucleotide-binding oligomerization domain-like receptors (NLR), NLR pyrin domain-containing 1 and 3 (NLRP1 and NLRP3), absent in melanoma 2, and caspase activation and recruitment domains domain containing 4 (NLRC4/IPAF)^[78]. Inflammasomes secrete caspase 1, which cleaves cytokine preforms, such as IL-1 β ^[79,80]. The activity of NLR is associated with autoimmune diseases, malignancies, inflammation, infection, and metabolic disorders^[59]. Inflammasome components expression levels are elevated in adipose tissue of obese mice^[81-83]. Conversely, NLRP3 and IL-1 β are decreased in low calorie dietary restriction^[83]. It seems therefore, that NLRP3 integrates multiple signals, causing pathogenic inflammation in obese subjects^[84]. Also NLRP6 has a critical role in gut homeostasis^[85,86]. Mice with non-functional NLRP6 develop an altered commensal system, preventing normal glycaemic control on a high fat diet and promoting NASH^[87].

In summary, there are at least two inflammasome types and substrates that can imbalance metabolism and inflammation in obesity^[85].

Linking obesity to cancer-inflammation is a double-edged sword

The role of chronic inflammation as a precursor of tumorigenesis can be observed in various cancers. A gastritis can give rise to gastric cancer, inflammatory bowel disease may promote colorectal cancer and patients suffering from a chronic pancreatitis may have a higher risk to develop pancreatic cancer^[88]. The inflammatory effect of adipose fat tissue might therefore be a general precursor of cancerogenesis. Like adipose tissue, tumor microenvironment is composed of multiple cell types like fibroblasts, epithelial cells, mast cells, and cells of innate and adaptive immune system that favor a pro-inflammatory, pro-tumorigenic environment^[89-91].

Contribution to the pro-inflammatory environment is the presence of macrophages that are attracted by MCP-1. Tumor tissue classically contains a high amount of M2 polarized macrophages^[92]. Macrophages activated by obese states, infiltrate tumors and amplify the inflammatory tumor environment through NF- κ B dependent cytokine production and angiogenic factors^[88]. Malignancies may be initiated or exacerbate by inflammation, and increased levels of inflammation may be a cause and/or a

consequence of malignancy^[88,93].

Steroid hormones

Production of steroid hormones in the adipose tissue are also relevant for various cancers: Steroid hormones such as progesterone, estrogen, androgens and adrenal steroids are associated with energy balance level and obesity associated development of several cancer types^[94]. In women, the BMI correlates with the incidence of breast cancer, endometrium cancer and other cancer entities that are associated to sexual hormone levels. The relative contribution of adipose tissue steroid hormone production to the whole steroid metabolism is about 100% in postmenopausal women^[44]. The risk of developing breast cancer in post-menopausal women enhances with an increase of circulating levels of steroid hormones such as dehydroepiandrosterone, testosterone, estradiol and estrogen, and low levels of sex hormone binding globulin. There is evidence that estrogens are mitogenic, regulating the expression of insulin, and inducing DNA damage by free radicals, genetic instability and gene mutations in cells^[95]. Increased estradiol levels can induce endometrial cell proliferation rates while inhibiting apoptosis and activating the IGF-1 synthesis in endometrial tissue^[5].

In men, testosterone has been the focus of most studies on sex hormones, obesity and metabolic complications. Evidence indicates that most tissues, including adipose tissue, express steroid converting enzymes necessary for the local production of androgens and/or estrogens^[96]. Up to 40% of the active androgen production (dihydrotestosterone) is accounted for by tissue conversion of adrenal precursors^[96]. In men, obesity has generally been associated with reduction of testosterone levels in plasma and elevated estrogen concentrations^[97-99]. It has also been reported, that men with visceral adiposity have decreased levels of testosterone^[100,101]. A growing body of interest suggests, that obese men are more likely to be diagnosed with aggressive prostate cancer and high tumor volumes^[102]. Furthermore, obese patients show a higher risk of cancer recurrence, as well as an increase in disease related deaths compared to lean patients^[103,104].

Hyperinsulinemia and insulin growth factors

Increased insulin levels and insulin growth factor-1 signaling enhance cancer development^[105]. Other observational studies reported an increased mortality of obese cancer patients with T2DM due to hyperinsulinemia and elevated IGF-1 serum levels. In contrast, patients with lower insulin, IGF-1, and IGF-2 levels showed a lower risk to develop cancer^[105-107].

Patients treated with insulin or drugs stimulating insulin secretion showed a significantly higher incidence of developing malignancies than those patients treated with anti-diabetic drugs like metformin. Therefore, metformin might be a potential anticancer agent^[108].

Caloric restriction, which causes down-regulation of circulating insulin and IGF-1 levels is a potent suppressor in carcinogenesis^[74]. Insulin and IGF-1 can trigger cell

growth and proliferation, while inhibiting cell survival *via* protein kinase B (Akt)/PI3K/mTOR (Akt/PI3K/mTOR) pathway^[73]. This signaling pathway is not only the most frequently mutated pathway in human cancers, it is also a signal mediator of leptin, adiponectin and pro-inflammatory cytokines^[46,109,110].

Caloric restriction reduces cancer incidence by inhibiting the Akt/PI3K/mTOR pathway *via* AMPK activation^[111-113]. In contrast, Kalaany *et al.*^[110] could show that tumors with PI3K activation do not respond to the anti-cancerous effects of caloric restriction.

Interestingly, mTOR activity is increased in obese patients. It plays a central role in obesity related inflammation. Multiple risk factors for cancer development in obesity have been identified, such as the insulin-IGF-1 axis, leptin/adiponectin, and pro-inflammatory cytokines like IL-6, IL-7 and TNF- α . These factors can activate multiple pathways including PI3K/Akt, MAPK and STAT3, resulting in increased mTOR activity. mTOR, however, inhibits the insulin-PI3K pathway by stimulating the STAT3 pathway^[46].

IL-6 and TNF- α play a major role in obesity associated hepatocellular carcinoma by activating the STAT3 pathway^[114]. The STAT3 pathway is involved in the regulation of various gene expressions including IL-17, IL-23, B-cell lymphoma 2, and vascular epithelial growth factor to promote cell survival, proliferation, invasion, angiogenesis, and metastasis^[115]. Consistent activation of STAT3 increases tumor cell proliferation, survival and invasion in suppressing anti-tumor immunity. STAT3 activation also leads to activation of further pro-oncogenic pathways, such as NF- κ B and the IL-6/Janus kinase pathways^[115].

FUTURE OUTLOOKS

As time passes, advancement of technologies proceeds

In 2003, the Human Genome Project was accomplished. After 13 years and estimated costs of 2.7 billion USD, the first human genome was sequenced. In contrast, the human genome of an individual was sequenced over a 5 mo period of time at costs of 1.5 million United States-Dollars in 2008^[116].

An overall trend in the public health sector is the tendency towards “individualized therapy” in order to tailor specific therapy options that are currently available for a given patient which is further supported by usage of sophisticated mouse models.

Without doubt, mouse models have helped to understand relevant pathways that are important in the regulation of human body fat on the molecular level^[117-123]. Initial insights into molecules that are important in regulating body fat, resulted primarily from genetic mouse screenings^[117,124-126]. The identification of specific inactivating gene mutations accompanied by an obese phenotype, have revealed that leptin, leptin receptor and melanocortin-4 receptor play central roles in the regulation of body fat^[127-132]. Interestingly, these three obesity phenotypes as a result of inactivating mutations, are also

relevant in humans, suggesting that knockout mouse models are a powerful tool to gain new insights into obesity relevant human genes and proteins.

A clinical approach might further support the *in vivo* findings that resulted from former obesity mouse models. Extensive tissue banking combined with collected clinical data may open up new perspectives in translational medicine as well.

There already exist several methods for screening large patient cohorts such as next generation sequencing. Also, established methods (*e.g.*, Fluorescence *in situ* hybridization or immunohistochemistry) became powerful tools when featured with high-throughput methods such as tissue microarrays to gain knowledge in the distribution of potential obesity relevant proteins. Tools such as laser mass spectrometry combined with a large tissue database in a microarray format might enable the initiation of virtual protein expression profiling of cells in their natural tissue environment. Further development in this field and others will open up new possibilities to identify causal links between gene expression levels, RNA modification, protein expression levels, post translational modification of proteins, intrinsic enzyme activity, and initiation and progression of diseases on a molecular level.

Automated chip technologies for detection of structural variation discoveries on a DNA- and RNA-level may decrease sequencing time, streamline sample preparations and reduce costs in future studies.

Acquiring great amounts of patient cohorts’ data in large databases combined with blood and tissue sampling will move clinical applicability of new gained knowledge into focus. New potential risk factors and/or therapy targets will be identified by high throughput tissue and blood screenings. Especially the combination of organ-tissue samples with respective blood samples, body fluids, and visceral/subcutaneous fat samples will help to understand complex causal connections between obesity and organ function failure and carcinogenesis on a molecular basis. The novel knowledge will be centralized and digitally organized, accompanied by its’ access that will be provided to health care units and hospitals for data reconciliation.

Preclinical and clinical patient screening will provide the basis for individualized digital patient DNA-, RNA-, protein-, post translational modification-, and enzyme activity profiles that automatically may be compared to already identified risk factors or therapy targets in centralized data bases.

In the present, there already exist research projects that might serve as landmarks for individualized obesity research in the future.

Interestingly, the TG and HDL Working Group were able to identify rare mutations that disrupt apolipoprotein C3 function by sequencing the protein-coding regions of 18666 genes in each of 3734 participants. By correlating loss of function studies with clinical data, carriers of these mutations were found to have a reduced risk of

coronary heart disease^[133].

In the future, these mutations might serve as clinical risk-markers for coronary heart disease in obese patients. Blood samples of obese patients could be easily tested for gene mutations and the presence of a mutation might then be interpreted as a protective factor in favor of the patients' health.

Another study conducted an association analysis of single nucleotide polymorphisms, identifying genetic variants that predispose to T2DM^[134]. Testing blood or tissue samples right after birth for these genetic variants might probably change the way of clinical diagnostics entirely.

In the future, patients with genetic predisposition for *e.g.*, diabetes might be diagnosed before the onset of disease. This knowledge could then lead to an individualized treatment in terms of dietary intake, physical exercise, or to earlier elective surgical intervention in obese patients.

Also, gut hormone and adipokine serum levels could be screened on regular basis in obese individuals. When out of balance, pharmaceutical intervention with suitable drugs such as GOAT- inhibitors, GIP-Receptor antagonists, inhibitors of the mTOR-, STAT3- and MAPK-, PI3K-pathways or even Metformin might be applicable in the future to prevent relevant comorbidities such as cancer.

Morbid obesity is already a widespread problem not only in first-, but also in second world countries. It causes various major chronic diseases such as coronary heart disease, diabetes, hypertension, and cancer. As living standards in second and third world countries enhance, morbid obesity will proceed to be a huge challenge for health institutions and national health systems. Obesity is a potential human health threat and is likely to become even more present in the future. The relevance and possible long-terms effects of maternal obesity to the health of the offspring are not fully understood. Studies that deal with this issue are of high relevance to precisely understand the long-term adverse health outcomes for the upcoming new generations.

In conclusion, there is an urgent need for obesity research with a straightforward concentration on new studies that aim to identify and interpret the complex, multifactorial variables in order to develop new therapy approaches and prevention programs for patients suffering from this disease.

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