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Ville Palomäki

MACROPHAGES IN HUMAN OBESITY

THE EFFECT OF LAPAROSCOPIC GASTRIC BYPASS SURGERY ON SUBCUTANEOUS ADIPOSE TISSUE INFLAMMATION

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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The effect of laparoscopic gastric bypass surgery on subcutaneous adipose tissue inflammation

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Abstract

Excess weight and obesity relate to multiple comorbidities, lost quality of life and mortality and cause major burden to healthcare and society. Most obesity seems to trace to changes in lifestyle and the food environment in the last few decades. The comorbidities related to obesity are increasingly viewed as a result of low-grade inflammation characterizing the state of excess adiposity. On microscopic level, this associates with the infiltration of immune cells, particularly macrophages, into adipose tissue. Bariatric surgery and weight loss repeal these alterations.

In this thesis, two behaviorally distinct macrophage pools are identified in subcutaneous adipose tissue of subjects with obesity. Of these, only the macrophages associated with pyroptotic adipocyte deaths decreased after laparoscopic Roux-en-Y gastric bypass for obesity. These macrophages were also highly imbued by known pro-inflammatory proteins, NLRP3 inflammasome and Caspase-1. The surgery associated with a shift of adipocyte size towards smaller populations.

In addition, a novel method was developed for fat cell size and count analysis using free open-source software.

Keywords: bariatric surgery, Caspase-1, crown-like structures, fat cell size, low-grade chronic inflammation, NLRP3 inflammasome, obesity

Palomäki, Ville, Makrofagit ja lihavuus. Vatsaontelon tähystyksessä tehdyn mahalaukun ohitusleikkauksen vaikutus ihonalaisrasvakudoksen tulehdukseen
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Tiivistelmä

Ylipainoon ja lihavuuteen liittyy lukuisia liitännäissairauksia, alentunut elämänlaatu ja lisääntynyt kuolleisuus sekä kasvanut terveyspalvelujen kulutus. Viime vuosikymmenten lihavuusepidemia selittynee ensisijaisesti länsimaalaistuneella elämäntavalla ja ruokaympäristön muutoksilla. Viime aikoina on herätty ylimääräisen rasvakudoksen aiheuttamaan matala-asteisen tulehduksen ja liitännäissairauksien yhteyksiin. Rasvakudoksessa tulehdus ilmenee erityisesti paikallisena syöjäsolujen eli makrofagien kertymisenä. Lihavuuskirurgia ja painonpudotus vähentävät sekä rasvakudoksen että elimistön yleistä tulehdustilaa.

Tässä väitöskirjassa tunnistettiin kaksi eri tavoin mahalaukun ohitusleikkaukseen reagoivaa makrofagiryhmää. Osoitamme, että ainoastaan rasvasolujen tulehdukselliseen hajoamiseen ja kuolemaan liittyvät makrofagit vähentyvät leikkauksen jälkeen muun makrofagimäärän pysyessä muuttumattomana. Erityisesti rasvasolujen hajoamiseen liittyvien makrofagien osoitettiin myös ilmentävän runsaasti tulehduksellisia NLRP3- ja Caspase-1-proteiineja. Leikkauksen jälkeen rasvasolujen keskimääräinen koko pieneni.

Kolmantena osatyönä esitetään uusi, ilmaista avoimen lähdekoodin ohjelmistoa käyttävä menetelmä rasvasolujen koon ja määrän mittaamiseen.

Asiasanat: Caspase-1, lihavuus, lihavuusleikkaus, matala-asteinen tulehdus, NLRP3-inflammasomi, rasvasolun koko

To family and friends

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Kuopio, May 2023 *Ville Palomäki*

Abbreviations

AT	adipose tissue
ATM	adipose tissue macrophages
BMI	body mass index
BPD	biliopancreatic diversion
BPD-DS	biliopancreatic diversion with duodenal switch
BPL	biliopancreatic limb
c.	circa
CCK	cholecystokinin
CI	confidence interval
CLS	crown-like structures
DAMPs	danger-associated molecular patterns
etc.	et cetera
e.g.	exempli gratia
EWL	excess weight loss
FC	fat cell
FCS	fat cell size
FFA	free fatty acid
GDP	gross domestic product
GIP	gastric inhibitory peptide
GLP-1	glucagon-like peptide-1
H&E	Hematoxylin and Eosin
i.e.	id est
IL-1β	interleukin-1β
IL-6	interleukin-6
IL-18	interleukin-18
LRYGB	laparoscopic Roux-en-Y gastric bypass
MCP-1	monocyte chemoattractant protein-1
NAFLD	non-alcoholic fatty liver disease
NFκB	nuclear factor-κB
NLRP3	nucleotide-binding oligomerization domain-like receptor-3
OA	osteoarthritis
OSA	obstructive sleep apnea
PAMPs	pathogen-associated molecular patterns
PCOS	polycystic ovary syndrome
PYY	peptide YY

RYGB	Roux-en-Y gastric bypass
SADI-S	single-anastomosis duodeno-ileal bypass with sleeve gastrectomy
SAT	subcutaneous adipose tissue
SD	standard deviation
T2D	type 2 diabetes
TG	triglyceride
TNFα	tumor necrosis factor α
TWL	total weight loss
U.S.A.	United States of America
VAT	visceral adipose tissue
VSG	vertical sleeve gastrectomy
WHO	World Health Organization

Original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Palomäki, VA., Lehenkari, P., Meriläinen, S., Karttunen, TJ., & Koivukangas, V. (2023). Dynamics of adipose tissue macrophage populations after gastric bypass surgery. *Obesity (Silver Spring), 31*(1), 184–191.

II Palomäki, VA., Väyrynen, JP., Koivukangas, V., Meriläinen, S., Karttunen, TJ., & Lehenkari, P. (2023). In human obesity adipose tissue NLRP3 is mainly found in macrophages. Manuscript.

III Palomäki, VA., Koivukangas, V., Meriläinen, S., Lehenkari, P., & Karttunen, TJ. (2022). A straightforward method for adipocyte size and count analysis using open-source software QuPath. *Adipocyte, 11*(1), 99–107

Contents

1 Introduction

In the last three or four decades, obesity and related comorbidities have reached pandemic proportions and are considered a major health concern worldwide (Ng et al., 2014; Rodgers et al., 2018; Zimmet et al., 2001). More than 2 billion adults are overweight (Finucane et al., 2011). Excess weight relates to myriad comorbidities, disability-adjusted life-years and mortality and poses a major burden to healthcare and the economy (Guh et al., 2009; MacMahon et al., 2009; Seidell & Halberstadt, 2015; Tremmel et al., 2017). The root causes of the obesity wave are complex and multifactorial. However, changes in lifestyle, eating habits, food availability and quality, physical activity, and labor requirements along with advances in food marketing coincidence temporally with the rise in obesity prevalence (Church et al., 2011; Drewnowski & Popkin, 1997; Rosiek et al., 2015; Swinburn et al., 2011).

Obesity associates with numerous comorbidities, such as type 2 diabetes, vascular diseases, sleep apnea, osteoarthrosis and even cancer (Felson et al., 2000; Frühbeck et al., 2013; Isomaa et al., 2001; Leitner et al., 2017; Young et al., 1993). Accumulating evidence supports the view that the detrimental effects of obesity relate to increases in local and systemic low-grade inflammation (Cottam et al., 2004; Johnson et al., 2012; Wellen & Hotamisligil, 2003). Both of these relate to adipose tissue level macrophage accumulation (Weisberg et al., 2003). On the other hand, bariatric surgery and weight loss associate with opposite outcomes: remission of comorbidities, decrease in macrophage infiltration to adipose tissue along with improvements in local and systemic inflammation status (Cancello et al., 2005; Cummings et al., 2004; Pinkney & Kerrigan, 2004; Pok & Lee, 2014).

In the present study, macrophage dynamics along with the known inflammatory mediators NLRP3 inflammasome and Caspase-1 were studied in subcutaneous adipose tissue of subjects with obesity and undergoing laparoscopic Roux-en-Y gastric bypass (LRYGB). Additionally, a novel method for measuring adipocyte attributes in histological samples was developed.

2 Review of the literature

2.1 Obesity epidemic

Obesity, i.e., accumulation of body fat to detrimental levels, has peaked to epidemic proportions not only in the developed world but also around the globe (*World Health Organization, 2022*; Zimmet et al., 2001; Ng et al., 2014; Abraham et al., 2016). It is estimated that nearly 2 billion adults are overweight and over 650 million of them are obese (Finucane et al., 2011; www.who.int). Obesity and overweight result in a considerable amount of lost and disability-adjusted life-years (Ng et al., 2014). Excess weight associates with numerous comorbidities and poses a major challenge to healthcare (Guh et al., 2009; Seidell & Halberstadt, 2015; Zimmet, 2000). The ensuing economic burden is likewise considerable (Tremmel et al., 2017). Tackling this complex and multidimensional matter in its entirety might be impossible, but any effort to at least alleviate the issue would unquestionably result in benefits for all.

2.1.1 History and evolutionary aspects of obesity

Human evolution diverged from the common ancestor with our closest living relative, chimpanzee, about 6–7 million years ago (Gagneux et al., 1999). In contrast to mainly herbivorous great apes, humans are omnivorous (Milton, 2003). It is argued that an increase in brain size and relative energy consumption in human evolution, perhaps at the expense of gastrointestinal tract size, promoted a dietary shift to favor more high energy-dense, easily digestible and concentrated foods (Armelagos, 2014; Milton, 2003). A large brain with a relatively large body size and an activity-requiring environment probably also necessitated foods from animal sources to be frequently accessed (Milton, 2003). However, accessibility to food and nourishment for early hunter-gatherer humans presumably varied in cycles of “feast and famine”, and the ability to store energy in the form of fat is generally, although not necessarily entirely, seen as a major adaptive feature of our species (Chakravarthy & Booth, 2004; Wells, 2006). According to current knowledge, modern humans emerged around 150-200,000 years ago in Africa and quickly migrated to new territories (Relethford, 2008). Seasonal food shortages, sometimes severe enough to cause starvation to death, have likely been a dominant selective force in human evolution even after the invention of agriculture, because

for agriculturists, cyclic shortages of food may have been even harsher (Wells, 2006). The ability to store energy as fat may also relate to the higher energy demand for reproduction as the ratio of brain to body size increased during the evolution of Homo species (Aiello & Key, 2002).

Taken together, it is easy to comprehend that evolutionary machinery, operating on tiny genetic variations and Darwinian (1859) natural selection, equipped man not only with efficient capability to seek out, find and consume food for energy, but also to store the surplus energy for the looming days of food scarcity. Evolution history perhaps preferred so-called "thrifty genes" in this matter (Neel, 1962). As a result, the main method that evolved to save energy to buffer its supply is to store it in the form of fat (Wells, 2006). However, the human habitat has changed, and mounting evidence now supports the view that genetic changes which once protected us during food shortages and unexpected environmental changes may now present susceptibility to metabolic syndrome and obesity (Johnson et al., 2013).

2.1.2 Prevailing wave of obesity

Obese individuals have always existed (Walley et al., 2006). However, the rising curve in the prevalence of obesity in the developed world dates to the late 1970s (Figure 1) (Ng et al., 2014; Rodgers et al., 2018). Obvious contributors such as increased calorie intake and changes in diet composition presumably play a major role in the rising prevalence of obesity (Astrup & Brand-Miller, 2012; Bleich et al., 2008; Drewnowski & Popkin, 1997). Food has become more easily accessible and affordable, and at the same time, more energy-dense, processed, and nutrient-poor (Swinburn et al., 2011). Unfortunately, energy-dense yet nutrient-poor foods tend to be those that are most inexpensive to produce and obtain, which may partly explain the emphasis of obesity in the lower socioeconomic groups (Armelagos, 2014; Drewnowski & Darmon, 2005). Along with diet, physical activity such as requirements of labor and overall activity has changed in favor of lower daily energy consumption (Badland & Schofield, 2006; Church et al., 2011). The living environment has changed profoundly from the prehistoric era in other ways as well. For instance, in recent decades, a promising branch of research has suggested that obesity is associated with profound changes in the intestinal microbial composition (Tilg & Kaser, 2011; Turnbaugh et al., 2006).

Interestingly, major advances in commercial and advertisement industry in the last 20–30 years seem to coincide with the obesity pandemic. It has been noted that

commercials and mass media have a prominent effect on our eating habits, and the time spent in front of a television or computer screen contributes to physical inactivity (Rosiek et al., 2015). Especially children may be particularly vulnerable to commercial influence (Aktaş Arnas, 2006). In a broader perspective, the consumption of food surpassing the metabolic needs may defy personal judgement and may even occur unconsciously (Cohen, 2008). It has even been argued that the knowledge of healthy choices is rarely motivating enough to induce any behavioral changes; instead, the behavior may better be explained, for instance, by social and group dynamics (Bloom, 2000). The widely held belief that health is solely determined by individual choice has even been deemed as a myth (Bloom, 2000).

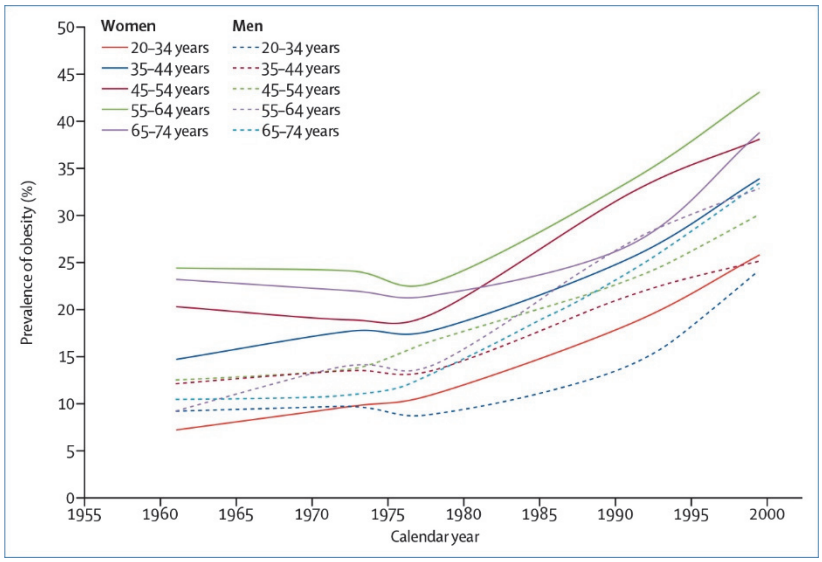

Fig. 1. Prevalence of obesity in the USA by age and sex (Rodgers et al., 2018). Reproduced under the terms of the copyright holders (CC BY NC ND).

2.1.3 Definition, etiology, and pathophysiology of obesity

Definition

The World Health Organization defines obesity and overweight as "the disease in which excess body fat has accumulated to such an extent that health may be adversely affected" (*World Health Organization.*, 2000). The traditional and WHO-

accepted measure of obesity is body mass index, which is calculated as weight in kilograms divided by squared height in meters (BMI, kg/m^2) (Dietz & Bellizzi, 1999; Flegal et al., 2013). BMI of 25–30 is considered as overweight and BMI over 30 as obese state (Table 1). Sometimes, BMI exceeding 50 is termed as super-obese in the literature (Gumbs et al., 2007). All-cause mortality seems to be lowest at BMI 22.5–25 kg/m^2 and median survival declines by 2–4 years at BMI 30–35 kg/m^2 and by 8–10 years at BMI 40–45 kg/m^2, mainly due to the associated vascular disease risk (MacMahon et al., 2009). However, negative implications on health start to accumulate gradually after a threshold of BMI 25 kg/m^2 (Field et al., 2001).

Although the obvious advantage of BMI in the assessment of obesity is simplicity, the definition is not without limitations. One clear criticism is that BMI does not necessarily indicate body fat percentage, distinguish between different fat deposits, or take into account muscle or bone mass (Nuttall, 2015). For instance, in a subject with BMI of 25, the fat percentage of body weight may vary from 14 to 43% when measured indirectly by bioelectrical impedance (Romero-Corral et al., 2008). Moreover, fat accumulation in the abdominal area, or so-called visceral fat, is more detrimental to health than fat in other deposits (Alvehus et al., 2010; Kissebah et al., 1982; Nguyen-Duy et al., 2003; Wajchenberg, 2000). However, as no simple, direct and accurate alternative is available at the moment, indirect methods such as bioelectrical impedance analyzer are currently used instead (Nuttall, 2015).

Table 1. Internal classification of adults based on body mass index.

Classification	BMI (kg/m^2)	
	Cut-off points	Additional cut-off points
Underweight	≤18.50	≤18.5
Severe thinness	≤16.00	≤16.0
Moderate thinness	16.00–16.99	16.00–16.99
Mild thinness	17.00–18.49	17.00–18.49
Normal	18.50–24.99	18.50–22.99
		23.00–24.99
Overweight	≥25.00	≥ 25.00
Preobese	25.00–29.99	25.00–27.49
		27.50–29.99
Obese	≥30.00	≥30.00
Class I	30.00–34.99	30.00–32.49
		32.50–34.99
Class II	35.00–39.99	35.00–37.49
		37.50–39.99
Class III	≥40.00	≥40.00

Source: WHO 1995, WHO 2000 and WHO 2004

Dietary composition, habits, and food energy density

As introduced previously, historical changes in the living habitat may have launched the current obesity epidemic. However, weight gain and obesity are a multidimensional and complex issue influenced by a vast range of factors such as inherited biological traits, early life experiences, environment, and social and behavioral factors (Morris et al., 2014).

Humans express only a weak ability to recognize energy-dense foods, which may lead to overeating in respect to healthy metabolic needs (Prentice & Jebb, 2003). Swinburn et al. (2009) suggested that the increased energy intake and caloric availability is more than enough to explain the current obesity epidemic at least in the United States of America (U.S.A.). Dietary habits have changed thoroughly;

larger portions and more frequent eating or drinking occasions account for most of the increase in daily calorie intake, although the energy density of the meals has risen as well (Duffey & Popkin, 2011). Special emphasis has been directed towards fast food and snack culture, recognized as a significant contributor and risk factor for obesity (Bowman et al., 2004; Bowman & Vinyard, 2004; Malik et al., 2006). Fast foods are infamous for their high energy density, and fast food consumption associates with high energy intake and increased risk for weight gain (Bowman & Vinyard, 2004). In contrast, consuming lower energy density foods relates to lower daily calorie intake (Rolls et al., 1999). In recent years, it has become a topic of conversation whether the obesogenic role of ultra-processed foods could be similar to that of the fast food industry (Poti et al., 2017). Furthermore, eating habits and dietary choices may largely be automated and subconscious, which easily leads to higher calorie intake than necessary (Mustajoki, 2015). The obesity pandemic may not just be a matter of individual lack of willpower but a consequence of ordinary peoples' normal response to an abnormal environment (Cohen & Farley, 2008; Mustajoki, 2015; Swinburn et al., 2011).

Physical activity

The role of physical activity in the obesity epidemic is under debate, although it seems to have a prominent effect. For instance, daily occupation-related energy expenditure has decreased over the past 50 years, and this may be related to an increased average BMI in the U.S.A. (Church et al., 2011). Likewise, the whole lifestyle is nowadays more sedentary, which associates with obesity (Smith Barnes et al., 2012). In respect of the latter, it has been demonstrated that environmental factors such as access and proximity of recreation facilities correlate inversely with the overall risk of obesity (Gordon-Larsen et al., 2006; Papas et al., 2007). Even simple things such as community design may have an effect; for instance, physical activity promoted by a walkable neighborhood may be reflected in the obesity risk (Frank et al., 2004). Exercise, in general, shows a dose-related effect on body weight and may result in healthier body composition, but due to the complexity of the mechanism of action, the individual responses are highly variable and overall long-term results are minimal or absent (Blundell et al., 2015; Westerterp, 2018). An environment encouraging physical activity provides protection against excess weight accumulation (Sallis & Glanz, 2009).

Food addiction and comfort eating

High caloric foods rich in sugar and fat are often palatable. It is suggested that along with regulation of food intake only by metabolic requirements, the hedonic and reward-seeking pathways drive behavior and may significantly contribute to development of obesity (Meye & Adan, 2014; Morris et al., 2014). Evidence exists for a theory that highly palatable foods may affect the mesolimbic dopamine pathways involved in reward-seeking behavior in a similar manner as drugs of abuse (Lutter & Nestler, 2009). For instance, subjects with obesity can display a different brain activation pattern than their lean counterparts in response to pictures of energy-dense foods (Stoeckel et al., 2008). These notions have raised the possibility that highly rewarding foods, particularly those enriched in sugar and fat, might lead to "food addiction" in some individuals (Morris et al., 2014). In animal experiments, rats develop an addiction-like behavior towards sugar and high sugar/high fat foods (Avena et al., 2005).

Chronic exposure to stress in rodents leads to reduced food intake; however, if palatable food is present the situation reverses (Morris et al., 2014). Moreover, even negative mood can affect the selection of foods and appetite (Hepworth et al., 2010). It is reasoned that due to an increase of dopamine activation in the limbic areas of the brain, rewarding food might dampen the hypothalamus-pituitary axis and inhibit the subsequent release of corticotropin-releasing hormone, thus alleviating stress signals in the body (Morris et al., 2014). The concept of "comfort eating" pattern is well-described in humans (Adam & Epel, 2007; Tomiyama et al., 2011). A clear association between chronic stress, abdominal obesity and higher BMI is also reported in the literature (Björntorp, 2001; Sinha & Jastreboff, 2013).

Genetics, epigenetics, and humoral regulation of obesity

The development of obesity is a multifactorial process and is significantly influenced by environmental factors. However, based on familial and twin studies, genetics might explain even 30–50% of the susceptibility to obese body phenotype (Bouchard, 1997).

The last few decades have shed light on the more specific genetic aspects of obesity (Martínez-Hernández et al., 2007). Genetic variances in obesity usually tend to affect homeostasis of energy intake and satiety mechanisms rather than metabolic phenotype (O'Rahilly et al., 2003). Obesity-related specific monogenic abnormalities usually associate with mutations in genes of humoral transmitters or

their respective receptors regulating appetite and satiety (Thaker, 2017). One of such transmitters is leptin. Leptin is secreted by white adipose tissue to convey information about the nutritional status to the central nervous system (CNS) and subsequently, to suppress energy intake and appetite (Friedman & Halaas, 1998). Consequently, congenital leptin deficiency associates with severe early-onset obesity (Montague et al., 1997).

Numerous other pathways and their dysfunctional states due to genetic aberration related to eating habits and energy homeostasis have also been characterized. The hypothalamic melanocortin system, consisting of multiple complex molecular interplays, also directs appetite, and has a critical role in energy homeostasis (Begriche et al., 2013; Girardet & Butler, 2014; Walley et al., 2006). For instance, a mutation in melanocortin receptor 4 is the most common cause of monogenic obesity in humans (Girardet & Butler, 2014). Another pair of noteworthy humoral agents are adiponectin and ghrelin. Like leptin, adiponectin is secreted from white adipose tissue and acts as a insulin sensitizer and is associated with the risk of metabolic syndrome and type 2 diabetes (T2D) (Heilbronn et al., 2003; Walley et al., 2006). Its concentration in blood is decreased in T2D (Heilbronn et al., 2003). In turn, ghrelin is known as "hunger hormone", providing a stimulus to food intake and growth hormone release, but it also has a role in glucose and energy homeostasis and even in muscle and bone metabolism (Pradhan et al., 2013).

In recent years, approximately 127 different sites have been linked to obesity in genome-wide linkage studies (Singh et al., 2017). In this respect, the knowledge of the genetic determinants of human obesity can be expected to increase vastly in the next few years. Interestingly, epigenetic factors such as alterations in DNA methylation or histone modifications, which affect the gene expression without changing the genetic code itself, may also play a role in obesity (Campión et al., 2009). For instance, high-fat diet induced the methylation in leptin promoter areas and decreased the circulating leptin levels in rats (Milagro et al., 2009). The role of genetics and humoral regulation in overweight and obesity is a vast and incredibly complex topic and cannot be addressed here in the way it deserves.

Medication-induced obesity

In addition to the overview presented above, a few other causative agents in obesity should be mentioned. It is well known that a high number of psychiatric medications, especially antidepressants and antipsychotics, are obesogenic (Ness-

Abramof & Apovian, 2005; Schwartz et al., 2004). On the other hand, common medications such as betablockers and thiazide-diuretics as well as antidiabetic and antiepileptic drugs can also cause weight gain (Verhaegen & Van Gaal, 2017). Corticosteroid therapy is infamous for its obesogenic effect (Curtis et al., 2006). The drug-induced weight gain often associates especially with visceral fat accumulation (Medici et al., 2016). In a meta-analysis, the magnitude of the effect of drugs was usually from a few kilograms up to a rise of 4–8% in body weight (Domecq et al., 2015).

Multiple mechanisms of action have been described in drug-induced weight-gain. For instance, insulin has a general anabolic effect and may stimulate the appetite due to hypoglycemia or fluctuations in glucose levels (Verhaegen & Van Gaal, 2017). Corticosteroid influences the hypothalamus and increases the intaking of dietary fats but also increases endogenous glucose production in the liver and affects food intake regulation via the endocannabinoid system, resulting in fat accumulation (Bowles et al., 2015; Christ-Crain et al., 2008; Dube et al., 2015). Betablockers, in turn, inhibit total energy expenditure and lipolysis by antagonizing adrenergic stimulation (Clément et al., 1995; Koch et al., 1981).

An unhealthy lifestyle is often associated with psychiatric illness; yet, the medication for the condition often correlates with weight gain (Verhaegen & Van Gaal, 2017). The exact mechanism for the weight-gaining properties of antipsychotics is not fully understood. The suggested mechanisms of action include the disruption of insulin signaling pathways and damage to pancreatic β-cells as well as medication-associated increase in the levels of free fatty acids and inflammation (Chen et al., 2017). In addition, antipsychotics generally affect dopaminergic and serotonergic neurotransmission, which are also involved in central appetite-regulation mechanisms (Himmerich et al., 2015). Of antiepileptics, especially valproate and carbamazepine are associated with weight gain through their actions on CNS and appetite regulation, the former affecting insulin release as well (Belcastro et al., 2013; Verrotti et al., 2011). Notably, gabapentin and amitriptyline, now widely prescribed as pain-stimulus modifying agents, increased weight by 2.2 kg and 1.8 kg, respectively (Domecq et al., 2015). The former exhibited its effect in just 1.5 months (Domecq et al., 2015).

2.1.4 Obesity-related comorbidities

Obesity is firmly related to multiple comorbidities, many of which are now thought to associate with low-grade inflammation (Bai & Sun, 2015; Cottam et al., 2004;

Hotamisligil, 2006). It is estimated that obesity alone could explain up to 44% of all diabetes cases and 23% of ischemic heart diseases (Fried et al., 2013; Frühbeck et al., 2013). Obesity associates with hypertension and certain types of cancer as well (Leitner et al., 2017). The relation of obesity and overall mortality is J-shaped, with a steepening rise in the latter after BMI of 30 kg/m^2 (Bhaskaran et al., 2018). However, even with strong correlation with obesity and comorbidities, the phenomenon is complex as not all obese patients have any evident metabolic impairment (Kramer et al., 2013).

Type 2 diabetes, insulin resistance and metabolic syndrome

Obesity poses a particular risk for T2D (Leitner et al., 2017). Conversely, most T2D patients are obese and have an excess of abdominal fat (Azuma et al., 2007; Jansen et al., n.d.). Excess and malfunctioning adipose tissue releases numerous secretions such as hormones, pro-inflammatory cytokines, glycerol and free fatty acids which are involved in the development of insulin resistance (Kahn et al., 2006). Fortunately, upregulation of pancreatic islet β-cell insulin secretion is usually able to compensate for the insulin resistance (Kahn et al., 1993; Polonsky et al., 1988). However, when the limit is exceeded, perhaps with contribution of simultaneously occurring β-cell dysfunction, the ability to maintain normal glucose levels is lost and T2D occurs (Kahn, 2001).

Insulin is considered a main anabolic hormone. It promotes the uptake of glucose from the bloodstream to liver, muscles and adipose tissue (Voet & Voet, 2011). In adipose tissue, insulin also stimulates triglyceride (TG) synthesis, the uptake of fatty acids and adipogenesis in general, and suppresses TG hydrolysis and the release of free fatty acids (FFA) (Boden, 2008; Saponaro et al., 2015). Insulin resistance in adipose tissue, on the contrary, associates with an increase in FFA in the bloodstream and β-cell dysfunction, thus aggravating whole body glucose homeostasis (Gastaldelli et al., 2017). Increase in FFA levels may also mediate the insulin resistance in muscle and liver (Rebrin et al., 1995; Roden et al., 1996). Obviously, insulin resistance at adipose tissue level impairs the capability to transport glucose into cells (Maianu et al., 2001). Visceral type of obesity seems particularly to associate with insulin resistance and risk of metabolic diseases, whereas femoral-gluteal type has a lower risk (Brochu et al., 2001; D'Adamo & Caprio, 2011; Klöting et al., 2010). Insulin resistance in muscle tissue is of importance as well and is considered by some authors as a primary defect in T2D

(DeFronzo & Tripathy, 2009). Impaired sensitivity to insulin effect in obesity affects the liver and kidneys as well (Meshkani & Adeli, 2009).

In obesity, this complex interplay with insulin resistance in various tissues and possible alterations in insulin secretion and glucose tolerance may long precede the onset of T2D and accompany other impairments seen in so-called metabolic syndrome, such as elevated blood pressure and dyslipidemia (Carr et al., 2004). In a given context of obesity, T2D and insulin resistance may be understood not as an individual disease but as the effect of environmental and lifestyle changes on human health (Zimmet, 2000).

Atherosclerotic cardiovascular disease, hypertension, congestive cardiac failure, and stroke

Obesity associates with a profound effect on vascular diseases. It is estimated that having metabolic syndrome poses a two- to three-fold risk for the development of cardiovascular disease (Isomaa et al., 2001). Visceral obesity, often accompanied by adverse lipid metabolism, associates particularly with compromised vascular health and hypertension (Rattarasarn et al., 2003; Ribeiro-Filho et al., 2003).

Obesity increases the risk for coronary artery disease, heart failure, and sudden cardiac arrest and death (Poirier et al., 2006). Abdominal obesity and features often related to it, such as low physical activity and eating habits, are listed as the most significant risk factors for myocardial infarction (Yusuf et al., 2004). Overweight and obesity increase the blood volume and the demand for cardiac output, thus predisposing to left ventricular hypertrophy and heat failure (Poirier et al., 2006). However, even lipotoxicity towards myocardial cells, via increased substrate provision to fatty acyl-coenzyme A and ceramide synthesis, is suggested (Zhou et al., 2000).

The majority of people with hypertension are overweight (Stamler et al., 1978). It is estimated that blood pressure and coronary disease risk increase by 3.0/2.3 mmHg and 12% for every 10 kg of excess weight, respectively (Poirier et al., 2006). Again, abdominal obesity comes with a higher risk (Björntorp, 1990). Obesity is thought to have a direct effect on hemodynamics by increasing blood and stroke volume; on the other hand, it increases peripheral resistance (Poirier et al., 2006).

Obesity is a well-documented risk for thromboembolic events (Hansson et al., 1999; Tsai et al., 2002). However, the association with pulmonary embolism was more evident in women (Goldhaber et al., 1997). Prothrombotic state in obesity,

along with other perturbations, may also relate to increased risk of stroke (Rost et al., 2001; Sriram et al., 2002).

It is estimated that the majority of the increase in mortality in obesity exceeding 40–45 kg/m^2 could be explained by the risks for vascular disease (MacMahon et al., 2009). Sadly, cardiovascular risks have even been reported in children with obesity (Poirier et al., 2006).

Fatty liver disease and obesity

Fat accumulation in the liver is closely associated with intra-abdominal fat content and is increased also in patients with T2D (Kotronen et al., 2007, 2008). The detailed mechanism of fat accumulation in the liver is debated (Jansen et al., 2013). However, one such mechanism could be that peripheral insulin resistance in adipose tissue drives the excessive release of FFA that are subsequently cleared from the bloodstream and stored by hepatocytes (Heilbronn et al., 2004). Interestingly, inflammatory changes in adipose tissue also seem to promote fat accumulation in the liver (Jansen et al., 2013; Lassailly et al., 2015).

Fat accumulation in the liver associates with non-alcoholic fatty liver disease (NAFLD) which increases the risk of mortality by 34% when compared to normal population (Adams et al., 2005; Browning et al., 2004). NAFLD may manifest as steatosis, steatohepatitis, or fibrosis of the liver (Lassailly et al., 2015). Progression of fibrosis results in cirrhosis of the liver and susceptibility to liver-related death (Adams et al., 2005; Matteoni et al., 1999).

Obstructive sleep apnea

Obesity is a significant risk factor for obstructive sleep apnea (OSA) with a prevalence in obese population (Ashrafian et al., 2012; Peromaa-Haavisto et al., 2017; Young et al., 1993). In OSA, transient upper airway collapses occur during sleep, which leads to frequent episodes of hypoxia and sleep fragmentation (Peromaa-Haavisto et al., 2017). Moreover, obese patients already have more demand for ventilation, respiratory muscle inefficiency, and lower functional capacity, which may further compromise the ventilation-perfusion rate (Strollo & Rogers, 1996). Alveolar hypoventilation is frequently observed in obesity (Strollo & Rogers, 1996). OSA associates strongly with increased cardiovascular risk and mortality, stroke risk, elevated blood pressure and decreased quality of life due to daytime sleepiness (Young et al., 2002).

Cancer

Cancer is among the leading causes of death in the world (Jemal et al., 2011; Siegel et al., 2012). In recent decades, obesity and overweight have been increasingly linked to the incidence of several cancer types and their prognosis (Cerdá et al., 2014; Parekh et al., 2012; Park et al., 2011, 2014; Vucenik & Stains, 2012). For instance, obesity is related to increased risk of cancers of the colon, esophagus, gastric, gallbladder, liver, pancreas, breast, endometrium, prostate and even leukemia (Pérez-Hernández et al., 2014; Vucenik & Stains, 2012). It is estimated that 15–20% of cancer deaths can be attributed to obesity (Pérez-Hernández et al., 2014)

The cancer-predisposing biological mechanism of obesity is not yet fully understood (Park et al., 2014; Vucenik & Stains, 2012). Nevertheless, several factors, such as chronic inflammation, insulin and the insulin-like growth factor axis, sex hormones and cytokines derived from adipose tissue are highlighted (Calle & Kaaks, 2004; Catalán et al., 2013; Park et al., 2014; Pérez-Hernández et al., 2014). Increased FFA levels in obesity may also function as an energy source for tumor cells or promote cancer pathogenesis (Nomura et al., 2010; Pérez-Hernández et al., 2014). Interestingly, adipose stromal cells from adipose tissue depots can even become recruited by various tumors to support the tumor microenvironment and tumor growth (Zhang et al., 2012).

The role of chronic inflammation in the development of malignancy has been documented in multiple types of cancer (Coussens & Werb, 2002). Moreover, in animal models, the inflammation also has an effect on the tumor progression (Balkwill et al., 2005; Karin, 2005, 2006). Curiously, even adipose tissue macrophages (ATM) can produce secretions which may modulate cancer cell phenotype (Mayi et al., 2012). Typically, proinflammatory ATM may secrete cytokines with tumor-promoting features, such as tumor necrosis factor α, interferon-γ, vascular endothelial growth factor, monocyte chemoattractant protein-1 and interleukins 1β, -6, -8, -18 or -32 (Catalán et al., 2013; Font-Burgada et al., 2016). Moreover, elevated circulating levels of many cancer-related proinflammatory cytokines are found in patients with obesity (Agrawal et al., 2002; Catalán et al., 2007, 2016, 2017; Weisberg et al., 2003).

In summary, obesity is a clear and confirmed, yet modifiable risk factor for cancer (Ahechu et al., 2018). In addition, it seems to have dose-response characteristics. For instance, it is estimated that the risk of colorectal cancer is

elevated by 2–3% for every unit of BMI increase (Ahechu et al., 2018; Giovannucci & Michaud, 2007; Sung et al., 2011).

Obesity and osteoarthritis

Obesity is a well-established risk factor for both the incidence and progression of osteoarthritis (OA) (Bliddal et al., 2014; Felson et al., 2000; Lementowski & Zelicof, 2008). Overweight associates with early degeneration of articular cartilages even before development of any OA symptoms, and obese patients are at higher risk of requiring knee or hip replacement surgery (Bliddal et al., 2014; Mezhov et al., 2014). For instance, having a BMI over 30 kg/m^2 associates with an almost 7 times greater risk for knee OA than weight in the normal range (Coggon et al., 2001). Risk of obesity for development of hip OA is lower compared to knee OA. However, an increase of BMI by 5 increases the risk of hip OA by 11% (Jiang et al., 2011).

Curiously, obesity also increases the OA risk of non-weightbearing joints in the hand and shoulder (Wall et al., 2020; Yusuf et al., 2010). Although the connection between obesity and osteoarthritis is certainly complex, involving increased stress on joints and altered biomechanics, systemic low-grade chronic inflammation and the pathology associated with it presumably also have an impact (King et al., 2013). Consequently, adipose tissue-derived pro-inflammatory mediators such as various adipokines and cytokines are implicated in the pathogenesis of OA (Wang & He, 2018).

Other diseases

Obesity associates with the risk of an overwhelming catalog of diseases in addition to the conditions described above. For instance, people with obesity are more likely to develop gallbladder disease, hyperuricemia and gout (Khaodhiar et al., 1999). Obesity increases the incidence of reflux disease and hiatal hernia (Anand & Katz, 2010; Hampel et al., 2005; Wilson et al., 1999). Women with obesity are more prone to menstrual irregularities and polycystic ovary syndrome (PCOS) (Escobar-Morreale et al., 2005; Pi-Sunyer, 1999).

Obesity is a noted risk factor for the development of major depression and general anxiety disorders as well (Gibson-Smith et al., 2016; Kasen et al., 2008). Excessive weight gain, insulin resistance, T2D and low-grade inflammation in general share many etiological factors, such as lifestyle and western style high-fat

diet, with various forms of dementia, e.g. Alzheimer's disease and vascular dementia (Selman et al., 2022).

2.1.5 Socioeconomic cost of obesity

Obesity relates to increases in annual healthcare costs of up to 36% and severe obesity may even double the costs, thus posing a considerable economic burden to societies (Finkelstein et al., 2008; Lévy et al., 1995; Sturm et al., 2013; Strum, 2002). As an example, according to modeling, in the U.S.A., obesity and related comorbidities incurred direct annual costs of $6,899 per capita in 2011 (An, 2015).

In addition to direct costs to healthcare, obesity has been estimated to inflict vast indirect expenses in the form of productivity losses due to lost work days, sick leave, disability pensions and mortality (Johannesson, 1996; Tremmel et al., 2017). Obese subjects had a two-fold risk for sick leave and three-fold risk for disability pension compared to their normal-weight counterparts (Narbro et al., 2002). In a study conducted among Swedish men, lifetime productivity losses associated with obesity were almost double compared to those of normal weight, premature death being a main contributor to the losses (Neovius et al., 2012).

The global economic cost of obesity was estimated at up to 2,000 billion dollars, equivalent to 2.8% of the global gross domestic product (Tremmel et al., 2017).

2.2 Treatment of obesity

Treatment of obesity should be a multimodal and wholistic exercise with special attention to patient's commitment and motivation towards therapy and lifestyle changes required (Lihavuus - Käypä Hoito-suositus, 2020). An overall paradigm shift towards viewing and treating obesity more like a chronic life-long illness is advocated (Sharma et al., 2018). Preventive measures may be more effective at the level of society.

2.2.1 Prevention of obesity

Prevention of obesity and related comorbidities should be addressed on both population and individual level. For instance, rigorous and continuing lifestyle interventions may prevent or postpone the onset of T2D in obese individuals (Lindström et al., 2003). However, lifestyle changes and conventional obesity interventions are difficult to sustain in the long term (Peromaa-Haavisto et al.,

2017). Likewise, general public preventive efforts targeted at individuals have only limited efficacy (Mustajoki, 2015; Swinburn et al., 2011).

However, the obesity pandemic could be fought with regulations and price policies (Mustajoki, 2015). For instance, smart food policies, e.g., tightening the tax policy on unhealthy food such as high-sugar soft drinks, affected the consumption of the target foods (Hawkes et al., 2015). Similarly, consumer marketing of unhealthy foods, soft drinks and candies could easily be regulated.

2.2.2 Conservative treatment of obesity

Conservative therapy of obesity should consist of a comprehensive lifestyle intervention and target weight loss, improving physical and mental health, and preventing or alleviating comorbidities.

A lifestyle intervention, implemented with sufficient intensity, to correct unhealthy eating behaviors and possibly, lack of physical activity, should be a first-line option in the treatment of obesity (Jensen et al., 2014). Even behavioral therapy, giving patients tools and techniques for adopting dietary and activity changes, may be of benefit (Jensen et al., 2014; Steinberg et al., 2013). Primary care physicians usually receive only limited training in nutrition and activity counseling (Antognoli et al., 2017). Thus, the option of referring patients to high-intensity community interventions such as Weight Watchers may be useful (Jensen et al., 2014). The efficacy of intense lifestyle modifications is demonstrated in study settings. For instance, a study aiming at coordinated 7% weight loss reduced the progression of impaired glucose tolerance to T2D by 58% (Knowler et al., 2002).

Unfortunately, maintaining the initial weight loss is difficult and some patients would benefit from continued support (Jensen et al., 2014; Perri et al., 2001). Long-term conservative therapies for obesity have a high failure rate and show only minimal efficacy (Kissane & Pratt, 2011; Picot et al., 2009; Sjöström et al., 2012).

Pharmacotherapy

Medication can be considered as an adjuvant in obese patients for whom conservative therapy such as diet and exercise have proven insufficient alone and who have BMI > 30 kg/m^2 or > 27 kg/m^2 with comorbidity (Apovian et al., 2015).

Various medications have been used for obesity. Orlistat is a pancreatic and gastric lipase inhibitor which induces fat malabsorption; at one year, orlistat-treated subjects lost 2.9 kg more weight than placebo-treated controls (Davidson et al.,

1999). Phentermine-topiramate combination releases norepinephrine and modulates GABA receptor signaling; it resulted in 8.8 kg more weight loss than placebo at one year (Gadde et al., 2011). Naltrexone-bupropion duo combines opioid receptor antagonist with dopamine and norepinephrine reuptake inhibitor, which resulted in 5 kg more weight loss than placebo in a one -year trial (Apovian et al., 2013).

Glucagon-like peptide-1 (GLP-1) analogs liraglutide and semaglutide are drugs which were initially used for the treatment of T2D but which have also demonstrated to have appetite- and weight-reducing effects in addition to improvements in glycemic control (Inzucchi et al., 2015; Meier, 2012). In a 56-week random controlled trial with subcutaneous liraglutide (3 mg daily), subjects lost 5.6 kg more weight than those in the placebo group (Pi-Sunyer et al., 2015). Subcutaneously administered semaglutide 2.4 mg once a week with lifestyle intervention resulted in a mean body weight reduction of 14.9% versus 2.4% with the placebo after 68 weeks of therapy (Wilding et al., 2021).

However, weight loss medications are not as popular as one might expect, perhaps due to only a moderate effect usually achieved (Yanovski & Yanovski, 2014). In general, termination of medication after 12–16 weeks should be considered if not at least 5% weight loss is achieved (Heymsfield & Wadden, 2017).

2.2.3 Surgical treatment of obesity

Bariatric surgery is currently more effective and reliable in long-term weight loss than conservative treatments (le Roux & Heneghan, 2018; Li & Richard, 2017; Sjöström et al., 2004, 2007). In addition to weight loss, the surgery reduces the risk of comorbidities such as cardiovascular risk and events, microvascular diabetes complications and cancer (Cummings & Rubino, 2018; Schauer et al., 2019; Sjöström et al., 2004, 2012). In most cases, bariatric surgery, sometimes termed ‘metabolic surgery’, induces remission of T2D (Cummings et al., 2004; Mingrone et al., 2015; Purnell et al., 2016; Schauer et al., 2017; Sjöholm et al., 2015). Resolution of the T2D and comorbidities is thought to involve an interplay of multiple organ systems such as the brain, liver, pancreas, muscle and adipose tissue (Pok & Lee, 2014). An association between bariatric surgery and decrease in mortality has also been shown (Adams et al., 2007; Arterburn et al., 2015; Christou et al., 2004; Flum & Dellinger, 2004; MacDonald et al., 1997; Sjöström, 2013).

The first bariatric procedures were initially designed in the 1950s with the purpose of achieving restrictive measures for the stomach and malabsorptive

component via bypassing part of the foregut, thus reducing the absorption of nutrients (Miras & Le Roux, 2013). This seems an oversimplification according to current knowledge. The modern view of the mechanisms of action also take into account the physiological changes after the procedure, such as increased release of satiety-associated and insulin action-enhancing gut hormones, such as GLP-1, and emphasizes the involvement of complex changes in gut-brain signaling altogether (Abdeen & le Roux, 2016; Batterham & Cummings, 2016). For example, a common bariatric procedure, Roux-en-Y gastric bypass (RYGB), works more by reducing hunger, increasing satiety and changing the preferences for food than simply relying on the principles of restriction and malabsorption (Miras & Le Roux, 2013). Nowadays, procedures are performed almost exclusively laparoscopically which reduces risks tenfold compared to open approach (Flum et al., 2009).

Roux-en-Y gastric bypass

The notion that partial resection of the stomach, particularly after Billroth II type operation, frequently led to weight loss inspired the development of gastric bypass by Edward E. Mason in the 1960s and 1970s (Mason, 2015; Mason & Ito, 1967). The technique has since undergone several modifications including mini-invasive approach (Lönroth et al., 1996; Rubino et al., 2010; Wittgrove et al., 1994).

The current approach is to create laparoscopically a 30–40 mL vertical gastric pouch from the upper stomach along the lesser curve using a linear stapler device and subsequently, anastomose it to the jejunum, typically 35–80 cm from the ligament of Treitz (Miras & Le Roux, 2013; Mitchell & Gupta, 2022; Olbers et al., 2003; Rubino et al., 2010; Salminen et al., 2018). Next, the created 'alimentary limb' is anastomosed to the biliopancreatic limb (BPL), usually in antecolic fashion, typically 75–150 cm from the gastro-jejunal anastomosis, thus restoring bowel continuity (Miras & Le Roux, 2013; Mitchell & Gupta, 2022; Olbers et al., 2003; Rubino et al., 2010). For a schematic drawing, see Figure 2A. The used lengths of Roux-en-Y limbs vary in the literature and lengthening the BPL may augment or at least hasten the weight loss and provide better metabolic control of comorbidities (Homan et al., 2018; Nergaard et al., 2014; Shah et al., 2019). In Oulu University Hospital, 80 cm and 150 cm are typically used for biliary and alimentary limbs, respectively. Average hospital stay is usually 1–2 days.

LRYGB commonly results in excess weight loss (EWL) by 51–68% in a setting where the equivalent of BMI 25 kg/m^2 is considered as an ideal body weight (Buchwald et al., 2004; Grover et al., 2019; O'Brien et al., 2019; Peterli et al., 2018;

Salminen et al., 2018, 2022). Improvement or even complete resolution of many obesity-related comorbidities is seen in the majority of patients (Buchwald et al., 2004). Remission of T2D is achieved in 70–84% of the patients and improvement in glucose metabolism may occur in just days or weeks after the surgery, i.e., even before significant weight loss (Buchwald et al., 2004; Cummings & Rubino, 2018; Pournaras et al., 2010). Approximately two-thirds of the patients who initially achieve the remission of T2D keep up the results in the long term and for the rest, median disease-free time is 8.3 years (Arterburn et al., 2013).

The detailed act mechanism of action of RYGB has been in the focus of attention. It is noted that endogenous gut hormone responses to a meal increase after the RYGB. For instance, postprandial GLP-1 and Peptide YY (PYY) responses rise in just days after RYGB (le Roux et al., 2007). Moreover, gut hormone responses correlate positively with the amount of post-surgery weight loss (Dirksen et al., 2013). Relative ghrelin deficiency after the surgery is also postulated (Pournaras & Le Roux, 2010). Ghrelin, a polypeptide hormone released by gastric and duodenal endocrine cells, is considered as the only appetite-stimulating substance produced by the gastro-intestinal tract (Casimiro et al., 2019). The effects of RYGB and vertical sleeve gastrectomy (VSG) on common gut hormones are presented in Table 2. Unlike ghrelin, many appetite and gastric motility-suppressing and satiety-inducing gut hormones such as GLP-1, PYY and cholecystokinin (CCK) are produced in endocrinously active L-cells residing in the ileum (De Silva & Bloom, 2012; Kuhre et al., 2021). Thus, bariatric surgery may result in enhanced stimulation on these cells and elevated gut hormone responses (Barreto et al., 2018).

Table 2. Common bariatric operations and gut hormones.

		Effect of surgery on fasting levels or postprandial rise	
Effect	Gut hormone	RYGB	VSG
Appetite stimulating	ghrelin	↓ ↔	↓ ↔
Appetite suppressing	PYY	↑	↑
	GLP-1	↑	↑
	CCK	↑↔	↑↔
	GIP	↑↔	↑↔

Abbreviations: PYY; peptide YY, GLP-1; glucagon-like peptide-1, CCK; cholecystokinin, GIP; gastric inhibitory polypeptide, RYGB; Roux-en-Y gastric bypass, VSG; vertical sleeve gastrectomy, ↑increases, ↓decreases, ↔ uncertain or conflicting data

Source: Barreto et al., 2018; Casimiro et al., 2019; Miras & Le Roux, 2013

However, it is likely that complex responses of multiple rather than a few gut hormones are required for increased postprandial satiation after RYGB (Ye et al., 2014). Increased satiety may also partly relate to vagal afferent neuronal stimulus from the pouch (Berthoud, 2008). The stimulus conveyed by a food bolus to alimentary limb mechanoreceptors may also be of importance (Abdeen & le Roux, 2016). Reorientation of the bowel with RYGB also results in alteration in enterohepatic circulation of bile acids. For instance, total plasma bile acid levels and availability in the distal intestine are increased, which may affect energy homeostasis and the release of gut hormones (Abdeen & le Roux, 2016; Katsuma et al., 2005; Pournaras et al., 2012). RYGB also alters the gut microbiota, which may have a role in weight loss effect (Liou et al., 2013). Curiously, experimental operations mimicking RYGB affecting intestinal physiology, but not gastric capacity, can eliminate T2D without or with little impact on weight loss (Cummings & Rubino, 2018).

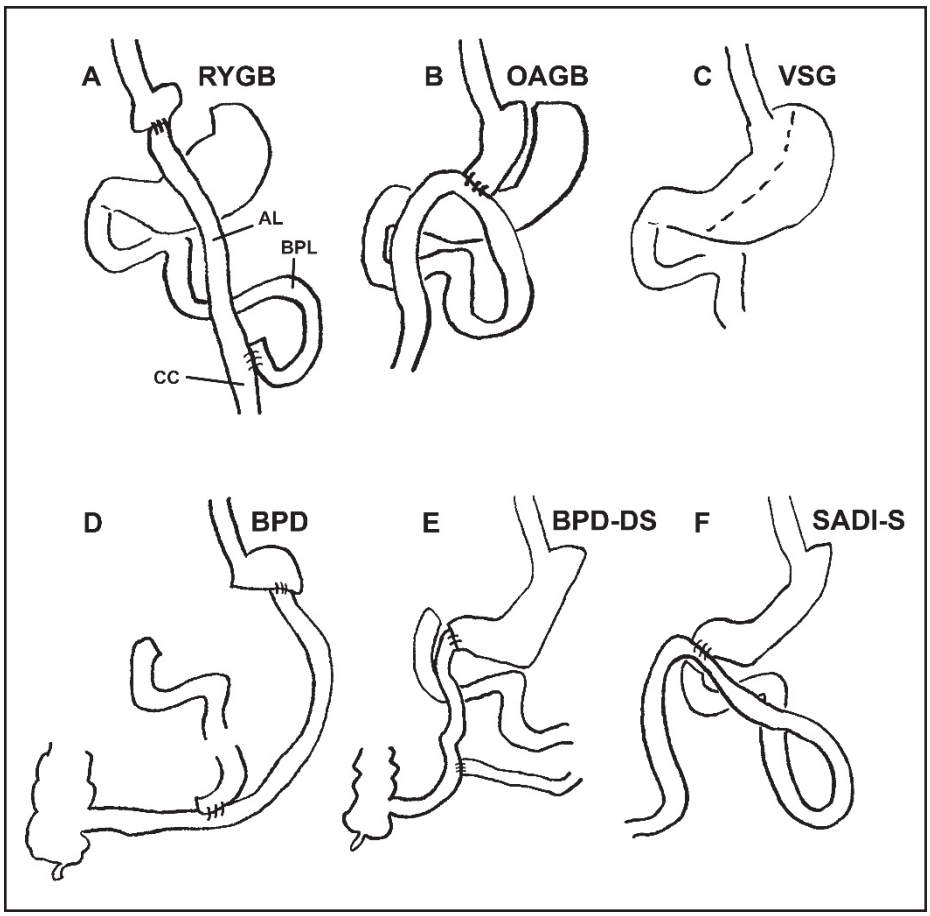

Fig. 2. A-F: Bariatric operations. A. Roux-en-Y gastric bypass. B. One-anastomosis gastric bypass. C. Vertical sleeve gastrectomy. D. Biliopancreatic diversion. E. Biliopancreatic diversion with duodenal switch. F. Single-anastomosis duodeno-ileal bypass. AL, alimentary limb; BPL, biliopancreatic limb; CC, common channel. Length of the limbs are not in scale. Illustration by Ville Palomäki 2022.

One-anastomosis gastric bypass

One-anastomosis gastric bypass (OAGB) (also known as single-anastomosis or mini-gastric bypass) was published by Rutledge et al. in 2001 (Rutledge, 2001). In the technique, a longer gastric pouch is created and anastomosed to the jejunum, typically 200–210 cm from the ligament of Treitz (Rutledge, 2001; Saarinen et al.,

2019). Thus, the technique utilizes a longer BPL and only one anastomosis compared to the standard LRYGB. For a schematic drawing, see Figure 2B. In terms of weight loss and control of comorbidities, the operation seems not inferior to LRYGB and is proposed as simpler, faster and safer to perform (Lee et al., 2005; Parmar & Mahawar, 2018; Robert et al., 2019). However, the longer BPL may predispose the subjects to nutritional deficiencies and diarrhea, although simultaneously offering a better control for T2D (De Luca et al., 2018; Robert et al., 2019). Concerns about bile reflux have also arisen (Saarinen et al., 2019, 2020).

Vertical sleeve gastrectomy

Vertical sleeve gastrectomy (VSG, Figure 2C) was initially developed as a first-step operation in biliopancreatic division with duodenal switch and later utilized as the first operation of a two-stage procedure for superobese patients (Carlin et al., 2013; Regan et al., 2003). In the procedure, the lateral aspect (70–80%) of the stomach is resected after mobilization with a linear stapler device, usually starting at 2–3 cm proximal from the pylorus (Jossart, 2012; Miras & Le Roux, 2013; Ramos et al., 2015). Fr 32–36 calibration tube is recommended (Jossart, 2012; Ramos et al., 2015). The operation is irreversible.

Despite being a purely restrictive procedure, profound changes in gastrointestinal physiology such as alterations in gut hormones are associated with VSG (Mans et al., 2015; Peterli et al., 2012; Yousseif et al., 2014). The method has become popular especially in the U.S.A. (Angrisani et al., 2015). The effectiveness of VSG in weight loss and comorbidity control is comparable to RYGB although the latter seems slightly more efficient (Dogan et al., 2015; Salminen et al., 2018, 2022; Yang et al., 2019). An endoscopic technique mimicking the VSG has also been described (Majumder & Birk, 2013)

BPD, BPD-DS and SADI-S

Various combinations of restrictive and malabsorptive components as a bariatric procedure have been described.

Scopinaro et al. (1979) described biliopancreatic diversion (BPD) in the late 1970s. In BDP, the proximal stomach, after a partial gastrectomy, is anastomosed to the distal 250 cm of the small intestine as sketched in Figure 2D. The remaining BPL is then anastomosed to an alimentary limb 50 cm proximal to the ileocecal

valve, thus forming a common channel only 50 cm in length (Deitel, 1998; Rubino et al., 2010; Scopinaro et al., 1979).

In biliopancreatic diversion with duodenal switch (BPD-DS, Figure 2E), sleeve-type gastrectomy is first performed as a first-stage operation. After some weight loss, the second operation is performed. There the first part of the duodenum is divided and the proximal part is anastomosed to the small intestine 250 cm to the ileocecal valve. The remaining BPL is anastomosed to the ileum to form a 100 cm common channel (Hess & Hess, 1998; Marceau et al., 1998; Rubino et al., 2010).

Single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) is a less complex loop variation of BPD-DS with one duodeno-ileal anastomosis slightly (2–3 cm) distal to the pylorus after dividing the first part of the duodenum (Figure 2F) (Kim, 2016; Sánchez-Pernaute et al., 2015). The length of the common channel has usually been 200–300 cm (Kallies & Rogers, 2020; Sánchez-Pernaute et al., 2010, 2015). However, a short common channel is associated with malnutrition and hypoalbuminemia, and recent recommendations suggest using a common channel of 300 cm or more (Topart & Becouarn, 2017).

BPD and BPD-DS result in up to 66–74% EWL, making them the most effective methods in bariatric surgery (Buchwald et al., 2004). However, the complexity of these procedures and concerns about long-term nutritional deficiencies have limited their popularity (Anderson et al., 2013; Kallies & Rogers, 2020). These methods may be considered for, e.g., superobese (BMI > 50) patients as one- or two-step primary operation or as a revisional operation after a failed previous operation (Anderson et al., 2013). SADI-S has in particular attracted interest. For instance, in comparison to RYGB, the mean total weight loss achieved with SADI-S was 38.7% vs. 28.7% with RYGB at 3 years and measures of T2D improvement were better with SADI-S (Torres et al., 2017). SADI-S may be very well suited for superobese (BMI > 50), metabolically highly impaired patients and has an obvious role as revisional surgery after failed VSG (Kallies & Rogers, 2020; Torres et al., 2017).

Gastric banding

In gastric banding, an adjustable/inflatable silicone band was placed around the upper stomach just below the GE junction to achieve restrictive measures (Burton & Brown, 2011; Miras & Le Roux, 2013). The technique became quite popular thanks to promising early reports in the 1990s, but the subsequently discovered

dismal cumulative (3–4% per year) major complication risk should disqualify the procedure as a sane alternative in bariatric surgery (Suter et al., 2006).

Safety and complications of bariatric surgery

Bariatric surgery has become safer over the last decades (Flum et al., 2009). Perioperative mortality rates are comparable to laparoscopic hysterectomy or knee arthroplasty and are lower than those of laparoscopic appendicectomy or cholecystectomy (Aminian et al., 2015). In meta-analysis of several randomized clinical trials the 30-day mortality was 0.08% (Chang et al., 2014). Cardiopulmonary complications such as pulmonary embolism or myocardial infarction are the major cause (70%) of perioperative mortality, although they are rare and occur in less than 1% of the cases (Flum et al., 2009).

The incidence of major early adverse events in the postoperative period is 4.3% (Flum et al., 2009). In the U.S.A., the National Registry perioperative complication rate for LRYGB was 3.4%, again less than for laparoscopic appendicectomy or cholecystectomy (Aminian et al., 2015). The most common early surgical complications involve anastomotic or staple line leakage (incidence 0.1–5.6%), bleeding (1.1–5%) and bowel obstruction (0.5–2%) (Brethauer et al., 2009; Nguyen et al., 2004; Rogula et al., 2007; Shikora & Mahoney, 2015; Thodiyil et al., 2008). Complication risk associates with male sex, smoking, higher BMI, older age, multiple comorbidities and revisional procedure (Flum et al., 2009).

Late complications in bariatric surgery may be of a surgical nature or present as nutritional deficiencies. After closure of all mesenterial defects, i.e., both mesenteric and Petersen's defects, the incidence of internal hernia is only about 1% (Geubbels et al., 2015). Closure of defects is advocated since it associates with lower incidence of internal hernia and late small bowel occlusion, although it may predispose to early occlusion due to kinking of the jejunojejunostomy (Magouliotis et al., 2020; Schweitzer et al., 2000; Stenberg et al., 2016). Petersen's defect should be closed as well (Apostolou et al., 2023). Trocar site hernia risk is negligible even without fascia closure (Johnson et al., 2006). Stenosis and margin ulcers develop in about 3–4% or even in up to 27% of the patients and can usually be treated with conservative or endoscopic means (Boza et al., 2012; Coblijn et al., 2014; Cottam et al., 2006; Espinel & Pinedo, 2012). A fistula between the pouch and remnant stomach after RYGB associates with weight regain, pain, marginal ulceration or even reflux symptoms and has a incidence of 1.2–6% (Chahine et al., 2018; Filho et al., 2006; Saeed et al., 2017).

Nutritional deficiencies are common in subjects seeking bariatric surgery even before the surgery; postoperatively, they relate to the malabsorptive effect of the operations (Schauer et al., 2016). Iron deficiency occurs in up to 50% of patients, followed by deficiencies in vitamin B12 (8–37%) and D (51%) (Cummings & Rubino, 2018; Schauer et al., 2016). Calcium and fat soluble vitamin deficiencies occur in 1–10% of the subjects (Schauer et al., 2016). Supplementation of vitamins and minerals is strongly recommended (Gong et al., 2008; Love & Billett, 2008; Marinella, 2008; Shankar et al., 2010). The most common complications and deficiencies after LRYGB are listed in Table 3.

Table 3. Incidence of complications after LRYGB.

Type	Complication	Incidence (%)	References
Early (<30-day)	30-day mortality	0.08–0.28	Buchwald et al., 2007; Chang et al., 2014
	Leakage	1.7	Thodiyil et al., 2008
	Bleeding	3.2–3.3	Nguyen et al., 2003; Schauer et al., 2000
Late	SBO or IH	1.27–3.1	Champion & Williams, 2003; Rogula et al., 2007
	Stenosis/ulcer	3–27	Coblijn et al., 2014; D. Cottam et al., 2006; Espinel & Pinedo, 2012
	GG-fistula	1.2	Chahine et al., 2018
Nutritional	Iron deficiency	6–50	Love & Billett, 2008
	B12 deficiency	26–70	Marinella, 2008
	Vitamin D deficiency	51	Schauer et al., 2016
	Calcium deficiency	10	Schauer et al., 2016

Abbreviations: SBO; small bowel obstruction, IH; internal hernia, GG-fistula; gastro-gastric fistula

Indications for bariatric surgery

Eligibility, criteria and recommendations for bariatric surgery in Finland follow international guidelines (Lihavuus - Käypä Hoito-suositus, 2020; Stegenga et al., 2014). The criteria and recommendations for patient selection are presented in Table 4. Patients should not have an active drug or alcohol addiction or a severe mental disorder. Profound consideration and psychiatric consultation are advised in case of an eating disorder. Smoking should be discontinued at least a month

before the surgery (Lihavuus - Käypä Hoito-suositus, 2020). Preoperative endoscopy is recommended for all patients prior to VSG and for those with predisposing risk for gastric pathology prior to gastric bypass (Saarinen et al., 2018).

Table 4. Criteria and recommendations for bariatric surgery.

Criteria	Additional criteria
BMI > 40 kg/m^2	
BMI > 35 kg/m^2 and	associated comorbidity expected to alleviate with the surgery such as T2D, obstructive sleep apnea, hypertension, PCOS, osteoarthritis in weight-bearing joints
BMI > 30 kg/m^2 and	T2D not manageable with conservative means
Age 18–65 years	(recommendation)

c. 5% weight loss during 6 months of conservative management and patient demonstration of adherence of lifestyle changes
Source: Lihavuus – Käypä Hoito 2020

Prognostic factors in bariatric surgery

A successful response to bariatric surgery has commonly been defined as at least 50% of EWL, in which BMI of 25 kg/m^2 is set as a reference point, (Al-Khyatt et al., 2017; Grover et al., 2019). However, it has been argued that percentage of total weight loss (TWL) could serve as a more accurate indicator and be less influenced by cofounding factors, such as initial weight (Brethauer et al., 2015; Corcelles et al., 2016; Grover et al., 2019; Sczepaniak et al., 2015; van de Laar et al., 2011). A suggested good response to bariatric surgery is at least 20% TWL at 1–2 years after the procedure (Corcelles et al., 2016; Grover et al., 2019).

However, depending on the definition, approximately 11–35% of the bariatric patients fail to reach a good weight loss response after the surgery (Brolin & Cody, 2007; Corcelles et al., 2016; Livhits et al., 2012; Parikh et al., 2007; Rawlins et al., 2011). A poor response may be associated with mechanical issues, such as leaving a gastric pouch that is too large, or subsequent dilatation of the gastric pouch (Campos et al., 2008). However, many patient-related factors have also been identified (Campos et al., 2008). Perhaps most frequently, higher initial BMI has

been reported as a negative predictor for suboptimal weight loss or weight regain after the surgery (Al-Khyatt et al., 2017; Chevallier et al., 2007; Giraldo Villa et al., 2013; Käkelä et al., 2014; Livhits et al., 2012; Magro et al., 2008). Older age when entering the procedure associates with modest outcome as well (Al-Khyatt et al., 2017; Cazzo et al., 2014). Overall comorbidity burden, and particularly T2D, has been linked to less weight loss in the follow-up (Al-Khyatt et al., 2017; Campos et al., 2008; Fox et al., 2015; Júnior et al., 2011; Kitamura et al., 2020). Psychological features or behavioral patterns such as depression, personality disorder or binge-eating habit are also noted as negative predictive factors (Hsu et al., 1998; Júnior et al., 2011; Livhits et al., 2012). Lower educational status and poor adherence to nutritional guidelines are likewise reported as negative predictors for less weight loss postoperatively (Júnior et al., 2011).

2.3 Obesity and low-grade inflammation of adipose tissue

Both systemic and adipose tissue level chronic low-grade inflammation characterize obesity (Wellen & Hotamisligil, 2003). On the other hand, the central role of inflammation in the detrimental effects of obesity and associated comorbidities is well known (Johnson et al., 2012). Many alterations seen at cellular level reflect the overall metabolic health and obesity-associated comorbidities, and dysfunctional adipose tissue may be viewed as a hormonally active organ mediating these effects via secretions such as cytokines and adipokines (Cottam et al., 2004; Hauner, 2004; Lago et al., 2007). As an example, the increased production of cytokines such as TNFα and IL-6 and MCP-1 is documented in proinflammatory adipose tissue and coupled with the development of insulin resistance (Lundgren et al., 2007; McLaughlin et al., 2008). Thus, obesity is not only a state of excess fat tissue but also an altered and dysfunctional state of adipose tissue biology (Goossens & Blaak, 2015; Knebel et al., 2017; Van Kruijsdijk et al., 2009).

2.3.1 Fat cell size

In obesity, adipose tissue depots grow via adipocyte enlargement (hypertrophy) or an increase in the number of cells (hyperplasia), or both (Laforest et al., 2015; Sun et al., 2011). In fat accumulation to SAT, hyperplasia generally associates with gynoid and healthier phenotype and hypertrophy with android and visceral type

obesity (Drolet et al., 2008; Joe et al., 2009; Kissebah et al., 1982; Rydén et al., 2014; Tchoukalova et al., 2010).

Mean fat cell size (FCS) rises in a curvilinear fashion with the body fat mass, reaching a plateau somewhere at BMI 30 kg/m^2 (Arner et al., 2010; Laforest et al., 2015). Curiously, the plateau is reached at c. 25 kg/m^2 for men and at c. 35 kg/m^2 for women, and the plateau is generally about 20% lower in omental fat than SAT only in women. (Laforest et al., 2015). Results between different measuring techniques vary. However, in histological analysis the mean adipocyte diameter at that plateau is 75–80 µm (Laforest et al., 2015). In other words, after reaching a certain level of obesity, further fat mass gain no longer affects the mean FCS.

Larger mean FCS is associated with metabolic impairment and comorbidities of obesity. For instance, higher abdominal SAT FCS predicted less healthy lipid blood lipid profiles in men and omental FCS predicted elevated TG concentration in both sexes (Hoffstedt et al., 2010; Imbeault et al., 1999; Veilleux et al., 2011). An association between SAT FCS and insulin resistance is also demonstrated (Arner et al., 2010; Cotillard et al., 2014; Despres et al., 1989; Haller et al., 1979; Kissebah et al., 1982; Lundgren et al., 2007; Monickaraj et al., 2012; Weyer et al., 2000). However, in many studies that adjusted the analysis by body fat distribution the correlations are no longer clear (Laforest et al., 2015). On the other hand, low levels of correlation may follow also if only severely obese patients, in whom FCS values have already plateaued, are studied (Laforest et al., 2015). Some studies have also demonstrated an association between the SAT FCS and liver fat accumulation or PCOS (Anand et al., 2011; Faulds et al., 2003; Heinonen et al., 2014; Koska et al., 2008; Larson-Meyer et al., 2009; Mannerås-Holm et al., 2011; Petäjä et al., 2013).

In conclusion, adipocyte size is influenced by not only the degree of obesity but also by sex and the anatomical localization of the fat deposit (Laforest et al., 2015). Moreover, in populations with severe obesity only slight FCS differences are seen as the mean cell size has already plateaued. With them, this may represent limited storage capacity of adipose tissue and other features, e.g., ectopic fat deposits, may become better indicators of metabolic health (Laforest et al., 2015).

2.3.2 Crown-like structures and macrophage infiltration

Macrophage infiltration in adipose tissue is associated with both local and systemic inflammation and metabolic impairments of obesity (Weisberg et al., 2003; Xu et al., 2003). For instance, in mice models of obesity, macrophages, but not other

immunological cells, dramatically upregulate and relate to obesity and adipose tissue inflammation (Xu et al., 2003). Macrophages in healthy adipose tissue are generally M2-polarized, whereas in obesity, the polarization turns toward pro-inflammatory M1 type (Lumeng et al., 2007; McNelis & Olefsky, 2014)

Fat cells can undergo an inflammatory-type programmed cell death which resembles pyroptosis (Cinti et al., 2005; Giordano et al., 2013). In adipose tissue, this results in arrangement of macrophages into so-called crown-like structures (CLS) around the leftover lipid droplet and remnants of dead adipocytes, presumably in order to sequester and clean up the debris (Cinti et al., 2005). This orientation of macrophages is viewed as a strong indicator of local inflammation or even a unique hallmark of adipose tissue inflammation (Haase et al., 2014; Wentworth et al., 2010). Formation of CLS and macrophage infiltration in adipose tissue relate to metabolic impairment in obesity and associate with elevated inflammation biomarker levels in plasma and insulin resistance (Camastra et al., 2017; Weyer et al., 2000). According to the literature, most macrophages in adipose tissue localize at the CLS sites (Cinti et al., 2005; Weisberg et al., 2003). Curiously, no correlation with the CLS appearance and FCS enlargement has been demonstrated in humans, indicating that the size of the adipocyte does not render it more susceptible to CLS-associated death (Aron-Wisnewsky et al., 2012; El Bouazzaoui et al., 2014; Jansen et al., 2013; Van Beek et al., 2014).

The weight loss in obesity improves the inflammatory status and alleviates obesity-related comorbidities (Cummings et al., 2004; Pinkney & Kerrigan, 2004). Two studies have evaluated the effect of bariatric surgery on CLS appearance. Cancello et al. (2005) studied 17 subjects undergoing LRYGB. They found that surgery-associated weight loss related to the reduction of macrophage infiltration and disappearance of CSL in adipose tissue. In another study, the CLS count also decreased among 13 subjects with obesity and T2D and 15 subjects with obesity without T2D (Camastra et al., 2017). Very-low-calorie diet-associated rapid weight loss seem to increase the CLS count at least in the short term (mean 45 days) (Alemán et al., 2017). In mice studies, the initial increased macrophage accumulation in the short term after applying caloric restriction was, however, followed by a long-term decrease in adipose tissue macrophage content (Kosteli et al., 2010).

2.3.3 NLRP3-inflammasome and Caspase-1

The immune system cells express a wide variety of different pattern-recognition receptors in order to sense surrounding danger signals. These signals include pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) (Li et al., 2021). Nucleotide-binding oligomerization domain like receptor-3 (NLRP3) inflammasome complex is one of the best characterized (Ahechu et al., 2018). NLRP3 activation is a two-step process. The priming step, mediated by, e.g., the NFκB pathway and toll-like or cytokine receptors, is followed by the danger signal triggered assembly of the NLRP3 inflammasome complex (Bauernfeind et al., 2009; De Nardo & Latz, 2011; Franchi et al., 2009). Many danger signals, such as extracellular ATP, adjacent necrosis, bacterial-derived molecular patterns, uric acid, cholesterol crystal ceramides and FFA have been discovered (Dostert et al., 2008; Li et al., 2009; Mariathasan et al., 2006; Pétrilli et al., 2007; Shen et al., 2021). Regarding the latter, saturated FFA, but not its unsaturated counterparts, seem to activate the NLRP3 pathway in macrophages in addition to other danger signals (Wen et al., 2011). Interestingly, unsaturated and omega-3 FFA can interfere with the activation by saturated FFA (L'homme et al., 2013; Yan et al., 2013).

Activated NLRP3 inflammasome functions as a platform for autocatalytic activation of procaspase-1 to form the active effector protein Caspase-1 (Dinarello, 2009; Kostura et al., 1989; Kuida et al., 1995; Martinon et al., 2002). Caspase-1 is an enzyme responsible for cleaving cytokine interleukin-1β (IL-1β) and interleukin (IL-18) precursors into their active forms (Schroder & Tschopp, 2010). IL-1β and IL-18 are critical pro-inflammatory cytokines which are widely involved in many local and systemic inflammatory reactions, such as host responses to infection, injury or other stress signals (Dinarello, 2009; Schroder & Tschopp, 2010; Sims & Smith, 2010; Voronov & Apte, 2015). Inflammasome activation relates to the development of many disease as well (Li et al., 2021). A schematic illustration of NLRP3 inflammasome action and contribution to metabolic diseases is provided in Figure 3.

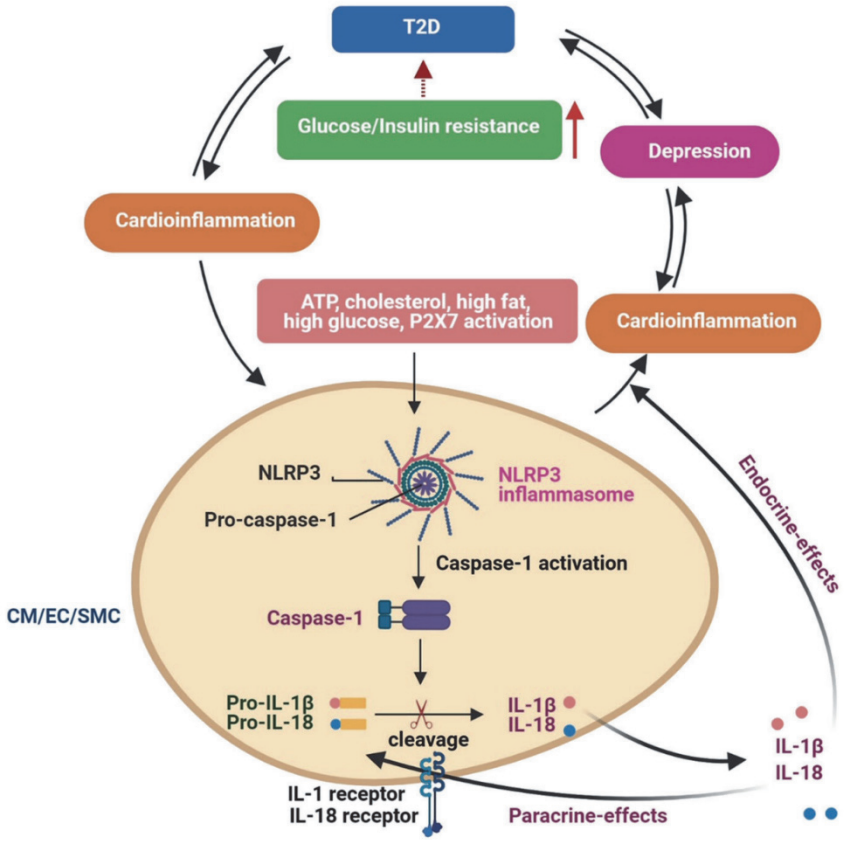

Fig. 3. A schematic drawing of NLRP3 inflammasome activation and contribution to disease development. Reproduced under the terms of the copyright holders (CC BY 4.0) (Li et al., 2021).

Role of NLRP3-Caspase-1 axis, IL-1β and IL-18 in obesity-related inflammation and comorbidities

IL-1β and IL-18 are known to exert many metabolic effects and associate with obesity and insulin resistance (Ahmad et al., 2013; Esposito et al., 2003; Skurk et al., 2005). On tissue level, IL-1β affects the phosphorylation of insulin receptor and increases the insulin resistance promoting TNFα expression (Ahmad et al., 2013; Esposito et al., 2003; Skurk et al., 2005; Strowig et al., 2012; Wen et al., 2012). Furthermore, in animal models, IL-1β or IL-1β-receptor knockout-mice are

protected from insulin resistance and NLRP3-deficient mice have insulin hypersensitivity (Haneklaus & O'Neill, 2015; McGillicuddy et al., 2011; Miura et al., 2010; Nov et al., 2013; Stienstra et al., 2010; Wen et al., 2011). Moreover, blocking IL-1β by pharmacological means has been shown to be beneficial in animal models of T2D and atherosclerosis (Bhaskar et al., 2011; Ehses et al., 2009). Adipose tissue also contributes to systemic IL-18 concentrations which are increased in obesity and correlate with metabolic syndrome and insulin resistance (Esposito et al., 2002; Hung et al., 2005; Murphy et al., 2016; Skurk et al., 2005).

NLRP3 inflammasome and related downstream effectors thus play a role in obesity and the associated insulin resistance (Zhou et al., 2010). NLRP3 in adipose tissue relates to body weight, T2D incidence and severity (Lin et al., 2014). For instance, Goossens et al. (2012) noticed that NLRP3 effector Caspase-1 mRNA was upregulated in SAT biopsies from obese individuals compared to their lean counterparts, and this correlated with insulin resistance and glucose intolerance. Vice versa, weight loss in subjects with obesity and T2D associated with the reduction of NLRP3 and IL-1β gene expression levels in SAT (Vandanmagsar et al., 2011). In obese mice adipose tissue, NLRP3 inflammasome colocalized strongly in macrophages and especially in CLS, and this activation was associated with insulin resistance (Giordano et al., 2013; Vandanmagsar et al., 2011). Furthermore, macrophages are known to produce insulin resistance-related cytokines IL-1β and IL-18 (Hotamisligil & Erbay, 2008; Jager et al., 2007; Vandanmagsar et al., 2011). Lastly, bariatric surgery mimicking RYGB in rats resulted in suppression of NLRP3 inflammasome activation in visceral adipose tissue and was reflected in improvements in glycemic control (Mocanu et al., 2015).

In addition to obesity and T2D, studies have linked NLRP3 to cardiovascular diseases and cancer as well (De Nardo & Latz, 2011). IL-1β-driven inflammation is associated with gastric inflammation and cancer as well as with colorectal cancer (Ahechu et al., 2018; Miki et al., 2004; Tu et al., 2008). IL-1β may also be involved in tumor invasiveness, angiogenesis and tumor-host interface (Apte & Voronov, 2002; Voronov et al., 2003).

In conclusion, NLRP3 inflammasome and its downstream cytokine products are affiliated in myriad diseases known to associate with low-grade inflammation, and especially with obesity and its comorbidities (Duewell et al., 2010; Masters et al., 2010; Stienstra et al., 2011). NLRP3 is expressed in adipose tissue macrophages and affects the obesity-related comorbidities (Vandanmagsar et al., 2011). Interplay between metabolism, NLRP3 and inflammation is now recognized as an emerging area in the research of metabolic diseases (Haneklaus & O'Neill, 2015).

3 Aims of the study

The present study analyzes histological inflammatory signs of SAT biopsies acquired from subjects undergoing bariatric (LRYGB) surgery or receiving conservative treatment for obesity. The specimens were collected in 2014–2019 in Oulu University Hospital, Finland, as part of a larger study assessing the role of bariatric surgery-induced weight loss in symptoms and development of OA and inflammatory markers.

The aims were:

1. To analyze the inflammatory changes, represented as macrophage infiltration and CLS density, in SAT following LRYGB or conservative treatment of obesity.
2. To analyze NLRP3 and Caspase-1 distribution in SAT of subjects with obesity.
3. To clarify whether baseline inflammatory changes predict the post-operative weight loss.
4. To formulate and validate a new method for adipocyte size and count analysis suitable for large, whole-slide analysis as well.

4 Subjects and Methods

4.1 Subjects, follow-up, and specimen acquisition

During 2014–2019, 122 subjects with obesity were recruited for the study in Oulu, Finland. Sixty patients were recruited among the patients who were scheduled for LRYGB and fulfilled the national criteria and recommendations for bariatric surgery (Table 4). The patients were referred to an internist for evaluation before the surgery and had a very-low-calorie diet for 3–5 weeks just prior to operation. The control group (62 subjects) was recruited among obese subjects who were listed in local public healthcare in a nearby region and were generally not interested in bariatric surgery. Subjects in the control group could participate in supportive meetings and receive nutritional guidance in public healthcare. Medications for related comorbidities were prescribed as indicated by the general practitioner. However, no specific program for conservative treatment was devised. Anthropometric data and medical history were acquired. Subjects were monitored for weight loss and comorbidities and surveyed with regular web-based lifestyle and quality-of-life questionnaires. The size of the groups was calculated assuming a difference of 11.6 between the groups in RAND-36 physical functioning score observed for knee arthroplasty and with assumption of 1/5 loss of the subjects during the first year. The Oulu University Hospital Ethics Committee authorized the study. Written informed consent was acquired from all subjects participating in the study.

A subcutaneous c. 1 cm^3 adipose tissue biopsy around the periumbilical area was acquired during the surgery and/or under local anesthesia at clinic appointments. Tissue samples were collected at 0 and 1 year for both groups. In the end, 39 and 43 consecutive paired samples were acquired for the surgery and conservative group, respectively. Missing data was attributable to, e.g., dropouts and refusals for minor incision under local anesthesia.

4.2 Histological staining and immunohistochemistry

The acquired biopsies were fixed in formalin and subsequently embedded in paraffin. Biopsies were sectioned at 5 μm and stained for Hematoxylin and Eosin (H&E) or appointed to immunohistochemical analysis. Macrophage marker CD68 and NRLP3 and Caspase-1 immunohistochemistry was conducted with BOND

Polymer Refine Detection System (DS9800; Leica Biosystems, Buffalo Grove, IL, USA) with 3,3′-Diaminobenzidine as a chromogen. Mouse monoclonal Anti-Human CD68 (1:200, Dako Agilent, Santa Clara, CA, USA) was used for 30 min with 20 min Tris-EDTA pretreatment. Multiplex staining was performed as previously described (Tsujikawa et al., 2017). For inflammasome NLRP3 and Caspase-1 immunohistochemistry, rabbit polyclonal anti-human NLRP3 (1:2000, Proteintech, Rosemont, IL, USA) and Caspase-1 (1:300, Abcam, Boston, MA, USA) were used. Instead of DAB, ImmPACT® AMEC Red (Vector Laboratories, Newark, CA, USA) was used as a chromogen in multiplex assay.

4.3 Image analysis

Stained sections were scanned with Leica Aperio AT2 (Leica Biosystems, Buffalo Grove IL USA) at 40 x magnification. Further analysis was carried out with QuPath 0.2.3 and ImageJ 1.53 with Adipocyte Tools plugin (Bäcker, 2012; Bankhead et al., 2017; Schneider et al., 2012). To measure baseline adipocyte size, count and densities, two 10E6 μm^2 sample areas from uniform adipocyte areas were first analyzed with Adipocyte Tools with manual correction of erroneous detections (if not omitted for comparative purposes in Study III). The basic settings for Adipocyte Tools were large cells, minimum size of 500 μm^2, and number of erosions rounds 3. Output data was processed in Excel software (Microsoft Corporation 2018). Adipocyte diameter was calculated assuming circular form for cross section. Density was measured in relation to the selected area under investigation.

Quantification of CD68 was measured with QuPath 0.2.3 open-source software employing its pixel classification feature. In short, annotated sections of 15 representative images were conjoined with the ‘create training image’ option. The pixel classifier was trained to detect CD68 positive areas reliably from other tissue. The trained classifier was applied to annotated adipocyte areas on whole-slide images to assess the amount of CD68-positive areas vs. other areas. CLS were manually counted and delineated to distinguish CD68 staining within them from the other staining presumably representing dispersed single-cell macrophages. CLS was defined as CD68-stained macrophage cluster surrounding at least 50% of dead adipocyte or lipid droplet and leftover debris (Bigornia et al., 2012). In comparative analyses, results are expressed in relation to 1,000 adipocytes in order to take into account the FCS changes after significant weight loss (Study I).

For Study III, H&E-stained images were assessed with QuPath 0.2.3. A pixel classifier based on random trees with high-resolution option was trained to

distinguish any tissue from the empty areas (dissolved fat). The trained classifier was then applied to annotated image sections of interest. The classifier's output detections were converted to annotation-type objects in QuPath 0.2.3 using the "Create objects" command with the following settings: min object size 20 μm^2, min hole size 30 μm^2, split objects, delete existing objects, and set new objects to selected. Data output such as adipocyte area and circumference were further processed in Excel spreadsheet software to calculate the diameter and pick the desired data according to the target area range (500 μm^2–100,000 μm^2). As things currently stand, QuPath does not have a direct feature for picking desired data according to the range limitation. In Excel, commands such as COUNTIFS and AVERAGEIFS were used instead.

4.4 Statistical analysis

Statistical analyses were conducted in SPSS for Windows (version 25, IBM Corp., Armonk, NY, USA). Graphs were also built in SPSS. Values are shown as mean and respective standard deviation (SD). Difference in paired values is accompanied by 95% confidence interval (CI). Normality of data was estimated with Shapiro-Wilk test. Student's t-test or Welch's t-test were employed for continuous independent variables and Mann-Whitney for non-parametric counterparts. Paired sample t-test or Wilcoxon Signed Rank were used for repeated measures for parametric or non-parametric variables, respectively. For bivariate analysis, Pearson correlation coefficient (r) or Spearman's correlation coefficient (ρ) were calculated for parametric or non-parametric variables, respectively. Two-tailed p-values are presented. Weight data was missing for 10/122 and 15/122 subjects at 0 and 1 year, respectively. FCS could not be acquired for 20/122 and 28/122 subjects at 0 and 12 months, respectively. In Study III, correlations of method outputs were illustrated with scatter and Bland-Altman plots. Intraclass correlation coefficient estimates and their 95% CI were calculated based on two-way mixed-effects model aimed at consistency.

5 Results

5.1 Study I

Baseline characteristics

The groups shared similar initial anthropometric characteristics and had a considerable prevalence of comorbidities (Table 5A). The majority of the recruits were women. Mean weight and BMI were slightly higher in the surgery group. Macrophage marker CD68 greatly facilitated the identification of CLS in adipose tissue (Figure 4).

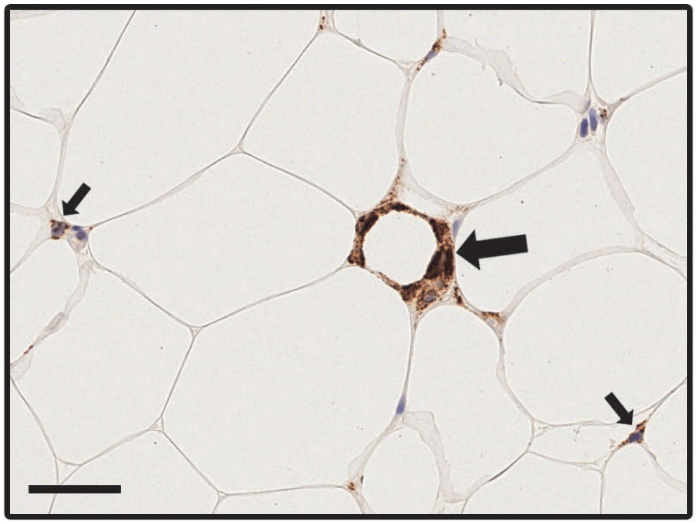

Fig. 4. Crown-like structure (CLS, large arrow) formed by a macrophage cluster and infiltrating single-cell macrophages (small arrows) in SAT. Immunostained for macrophage marker, CD68. Scale bar 50 µm. Figure by Palomäki et al. 2022.

Baseline mean FC density, CLS density, and mean CD68+ (μm^2) dispersed outside of CSL, i.e., presumably in infiltrating single-cell macrophages for every 1,000 FC along with CD68 proportion in CLS vs. all staining, are represented in Table 5B. At baseline, the amount of CD68+ in infiltrating macrophages had a moderate correlation to CSL density ($\rho = 0.53$, $p < 0.001$, R^2 0.294). No significant bivariate correlations were found between CLS density or infiltrating macrophage staining

and gender, age, initial BMI, smoking history, T2D prevalence or mean FCS. However, the proportion of large (70–89 μm) FC had a weak negative correlation with CLS density ($\rho = -0.248$, $p = 0.025$, R^2 0.032). As a group, subjects with T2D had larger mean FCS (77.2 SD 9.0 vs. 72.3 SD 8.0) and thus smaller FC density (163.2 SD 30.4 vs. 180.7 SD 39.5 cells/10E6 μm^2) than their non-diabetic counterparts.

Effect of LRYGB or conservative treatment on weight, FCS, CLS density and dispersed single-cell macrophages in SAT

After 12 months, weight, BMI and TWL% decreased only in the surgery group (Table 5B). In the surgery group, TWL% for non-diabetics was 24.2 (SD 6.5) and for subjects with initial T2D, 16.6 (SD 4.6) ($p < 0.000$). FC density increased and distribution shifted towards smaller populations only in the surgery group (Table 5B, Figure 5).

CLS density declined in the surgery group by 3.0 per 1,000 FC (CI 1.8–4.2) and was lower than in the conservative group at 12 months (Figure 6A). CLS density increased in the conservative group from 3.2 (SD 2.3) to 4.2 (SD 3.3) ($p = 0.07$). LRGYB did not affect the amount of staining in infiltrating single-cell macrophages, although single-cell macrophage infiltration increased in the conservative group. (Figure 6B). The proportion of CD68+ within CLS vs. all CD68 staining in the surgery group decreased below the conservative group even though it was initially higher (Figure 6C).

Table 5. Baseline anthropometrics (A) and evolution of basic measurements, FC density, CLS density, dispersed CD68+ single-cell macrophage population and % of CD68+ in CLS vs. all tissue (B).

A Baseline anthropometrics	Surgery		Conservative	
n	60		62	
Sex (F/M)	51/9		51/11	
Age (years)	48.5 (8.2)		50.9 (8.0)	
Height (cm)	166 (6.5)		166 (7.9)	
Hypertension	47.4%		48.4%	
T2D	33.3%		25.8%	
OSA	21.7%		21.0%	
B evolution of measurements	0 months	12 months	0 months	12 months
Weight (kg)	117 (19.5) *	91.5 (16.8) ***	110 (17.3) *	109.6 (17.2)
BMI (kg/m^2)	42.4 (6.5)	32.9 (5.7) ***	40.0 (5.0)	39.8 (4.6)
TWL%		21.9 (6.8) ***		0.1 (4.1)
FC (cells/10E6 µm^2)	182.6 (36.1)	225.9 (46.3) ***	169.7 (37.7)	182.4(42.4)
CLS/1000FC	4.1 (3.6)	1.1 (0.8) [a b]	3.2 (2.3)	4.2 (3.3) [b]
disp.CD68(µm^2/1000FC)	12.0 (7.2)	11.0 (5.3) [b]	11.9 (6.6)	16.4 (10.5) [a b]
% of CD68+ in CLS	20.2 (12.6) [b]	4.1 (3.0) [a b]	13.0 (9.8) [b]	12.0 (9.2) [b]

Values are mean (SD)

* = p = 0.037 for Mann-Whitney test between the groups

*** = p < 0.001 for paired sample t-test vs. initial value

a = stat. significant difference vs. initial value (see Fig. 6)

b = stat. significant difference between the groups (see Fig. 6)

Abbreviations: T2D; type 2 diabetes, OSA; obstructive sleep apnea, TWL; total weight loss, FC; fat cell, CLS; crown-like structures

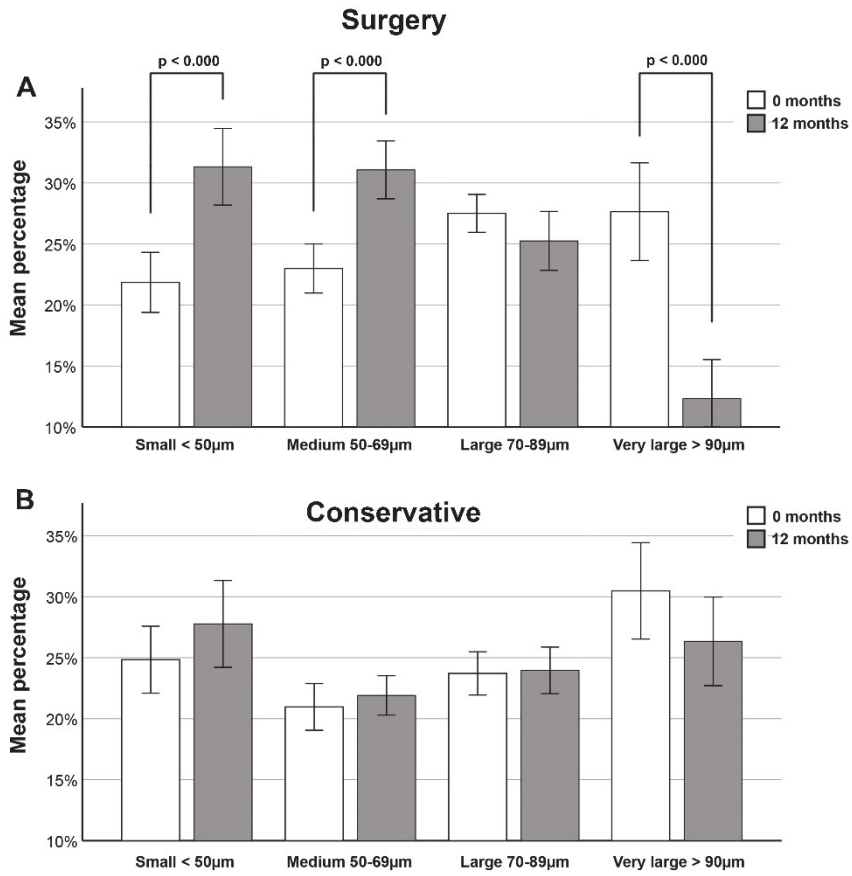

Fig. 5. Fat cell size distributions according to the mean diameter (paired sample t-test) in the surgery and conservative groups at 0 and 12 months. Reproduced under the terms of the copyright holders (CC BY-NC 4.0) (I).

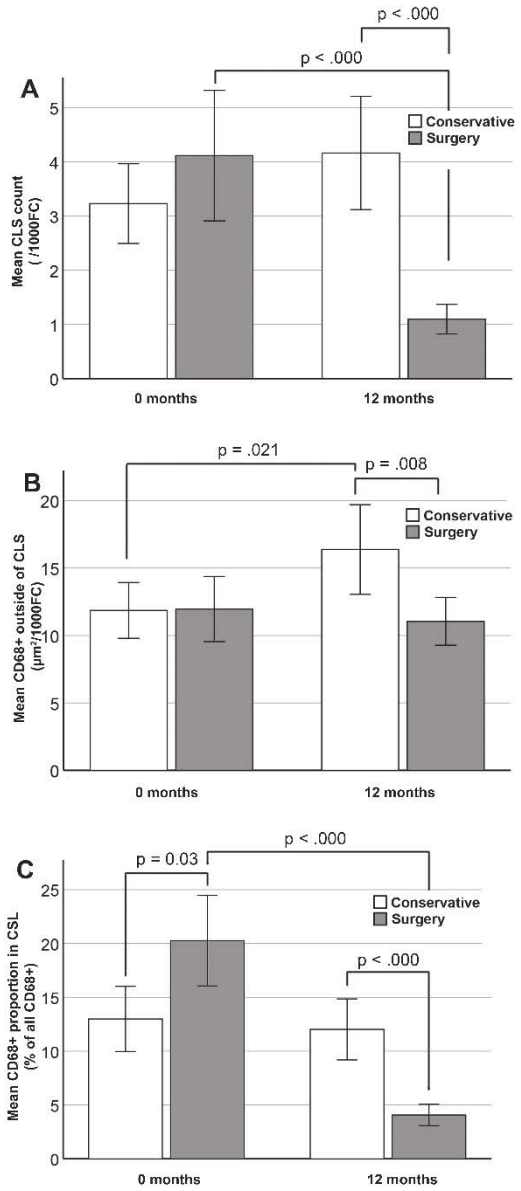

Fig. 6. Effect of LRYGB vs. conservative treatment on CLS density in SAT (A) and on infiltrating single-cell macrophages outside of CLS (B) and on CD68+ proportion within CLS vs. all CD68+ (C). Reproduced under the terms of the copyright holders (CC BY-NC 4.0) (I)

Relationship of weight loss magnitude and macrophage populations in the surgery group

Only the subjects in the surgery group achieved any meaningful weight loss. At 12 months, 64.7% achieved TWL > 20% while 35.3% were below. The TWL > 20% vs. TWL < 20% subgroups had no differences in CLS density, the amount of infiltrating single-cell macrophages or CD68+ distribution in vs. outside of CLS or in FCS measurements at any time point (Figure 8A-C, FCS data not shown). Correlation analyses could not detect any significant associations between these measurements and the extent of weight loss or change in BMI. However, in both weight loss responder groups, CLS density and CD68+ proportion in CLS declined in similar fashion (Figure 8A and 8C). In other words, the decrease in CLS density in the suboptimal weight loss responder group was similar to that in the good responder group (Figure 7, scatter plot).

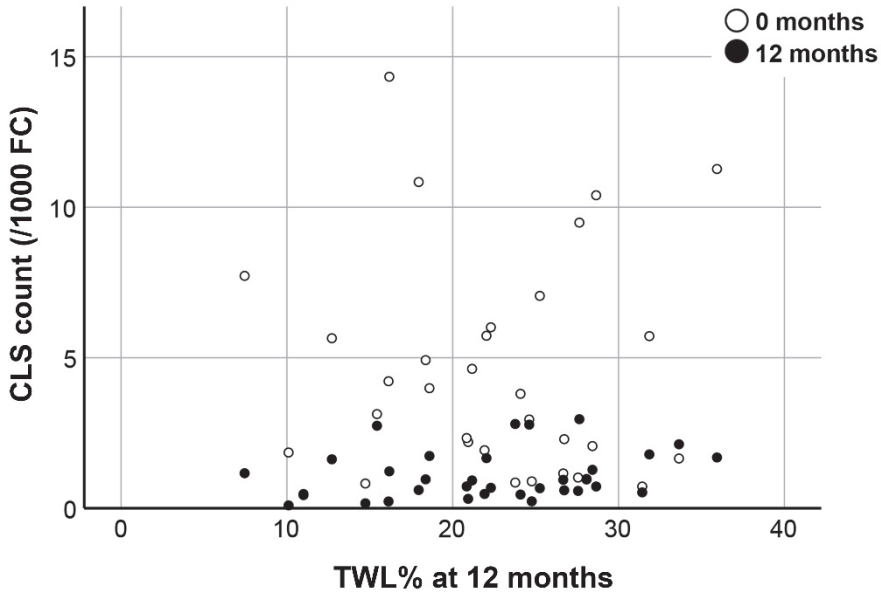

Fig. 7. CLS density after LRYGB decrease in similar fashion even in subjects achieving suboptimal (total weight loss < 20%) weight loss. Reproduced under the terms of the copyright holders (CC BY-NC 4.0) (I).

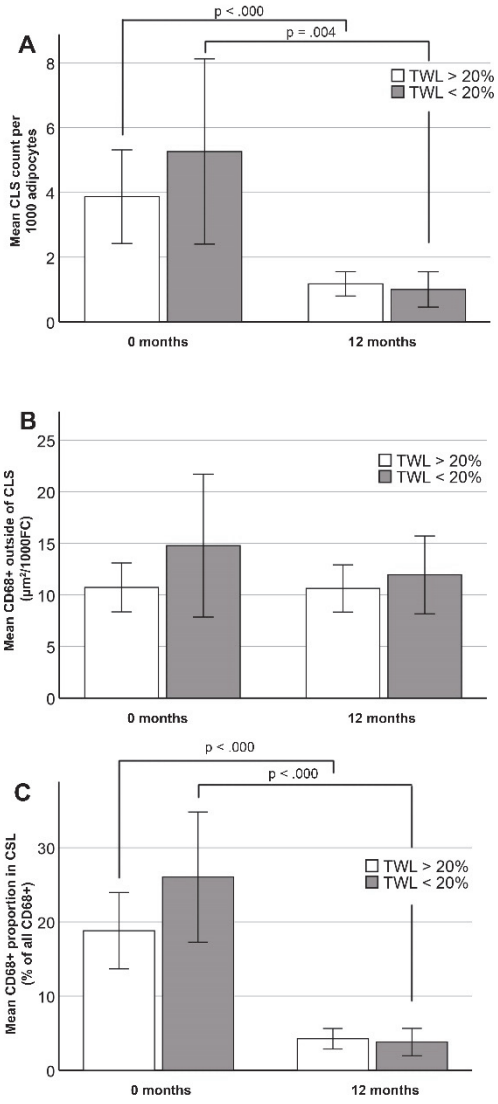

Fig. 8. Evolution of CLS density (A), infiltrating singe-cell macrophage amount (B) and CD68+ proportion within CLS vs. all CD68+ (C) in good (TWL > 20%) or suboptimal (TWL < 20%) weight loss responders after LRYGB. Reproduced under the terms of the copyright holders (CC BY-NC 4.0) (I).

5.2 Study II

NLRP3 and Caspase-1 localize predominantly in SAT macrophages

Whole-slide sections stained with NLRP3 and Caspase-1 immunohistochemistry were studied in detail. Both NLRP3 and Caspase-1 antibodies were predominantly found in CLS and single-cell macrophages in a similar pattern as CD68 staining of SAT sections (Figure 9, left panel). NLRP3 and Caspase-1 also stained the endothelium in vascular structures, whereas CD68 staining in these was rather sporadic and probably represented single cell macrophages (Figure 9, right panel). Multiplex staining of the same sections confirmed the overlapping staining in single-cell infiltrating macrophages and in CLS (Figure 10). In multiplex staining, the previous antibody is chemically removed after digitizing the slide and the immunohistochemistry is then repeated with another antibody of interest. A negative control, i.e., omitting the primary antibody but applying the secondary, confirmed the adequate removal of the first staining.

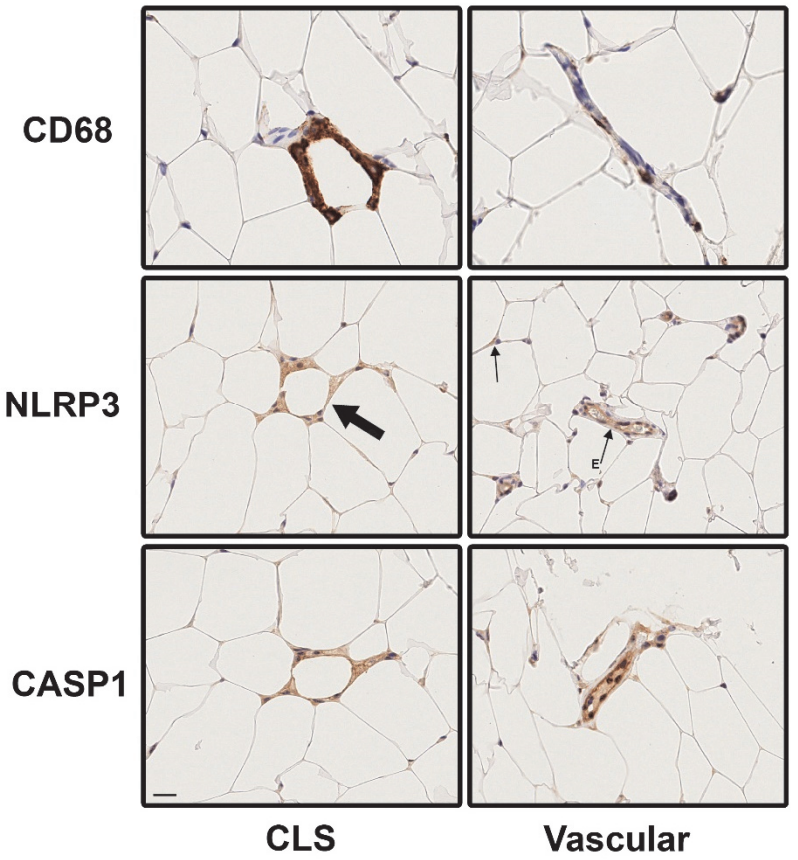

Fig. 9. NLRP3 and Caspase-1 localize predominantly in macrophages (small arrow) of SAT and are particularly concentrated in CLS (large arrow). Some contiguous staining is also found in the endothelium (small arrow + E) whereas CD68+ in capillaries is blotched and presumably represents macrophages/monocytes. Scale bar 20 µm. Figure by Palomäki et al. 2023.

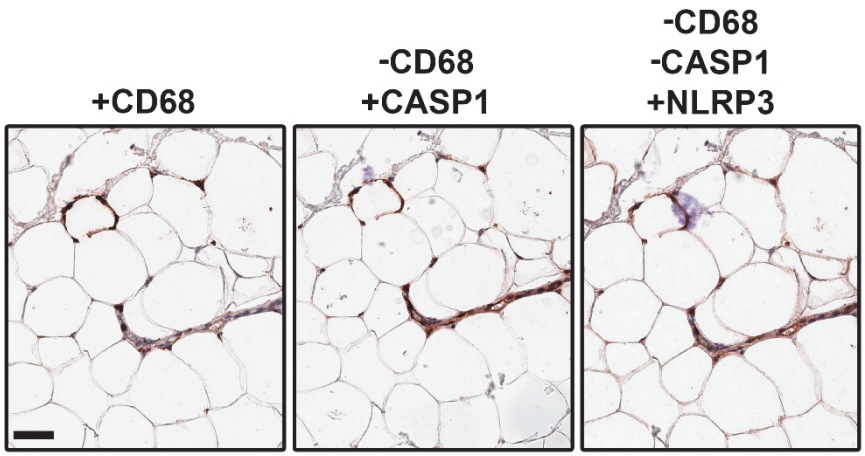

Fig. 10. Multiplex immunohistochemistry was utilized to assess staining of macrophage marker CD68, Caspase-1 and NLRP3 in the same adipose tissue sections. Similar generally overlapping staining in these consecutive staining steps was observed, although Caspase-1 and NLRP3 was also found throughout the endothelium. Scale bar 50 µm, + ; antibody added, - ; antibody removed. Figure by Palomäki et al. 2023.

A proposal for CSL lifespan

The purpose of macrophage dynamics leading to the formation of CLS is presumably to execute sequestering and clearance of leftover lipid droplets and other debris, i.e., a scavenger response. The time span of the phenomenon is from days to weeks. However, during the review of stained sections it became apparent that the specimens contained CLS in different phases of their lifespan. A proposal for these phases is depicted in Figure 11. First, macrophages encircle the fat cell which has not yet lost its form. In the next phases, the visible lipid droplet is gradually engulfed, leaving just a cluster of macrophages. The “CLS remnant” in the last phase was still enriched with NLRP3 and Caspase-1 staining.

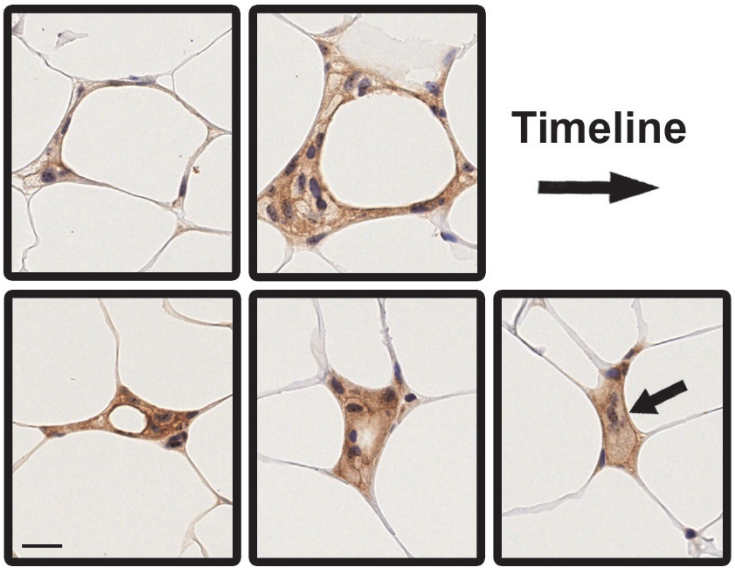

Fig. 11. Proposal for different phases of CLS lifespan. First, macrophages encircle the adipocyte. The lipid droplet is gradually consumed; eventually, just a macrophage cluster or "CLS remnant" (arrow) remains. Immunostaining for Caspase-1. Scale bar 20 µm. Figure by Palomäki et al. 2023.

5.3 Study III

Detection of fat cells with QuPath and ImageJ with Adipocyte Tools-plugin

In study III we developed a novel method for measuring adipocyte size and count using free open-source software QuPath 0.2.3. As a test material for validating the method, we used 60 scanned whole-slide images of H&E-stained baseline SAT samples from the obese subjects participating in the study. The mean BMI in this group was 39.01 kg/m^2 (SD 5.67 kg/m^2). First, QuPath's pixel classifier was trained to distinguish H&E-stained areas from the empty areas which represented mainly dissolved fat inside the FC. The classifier was visually evaluated against the material. We found that the success of rendering adipocytes correctly depended on the quality of the original H&E-staining. However, a benchmark method, ImageJ with Adipocyte Tools-plugin, was not much better in handling poorly stained sections. An arbitrary visual scale of good-average-poor applied along with

Adipocyte Tools rendering of the same images is demonstrated in Figure 12. Poor rendering of the images presumably reflected suboptimal processing of the specimens during fixation, cutting or staining the sections, and alternatively, training of the pixel classifier could not overcome the issue (Figure 13). Finally, average and good samples were used to validate the QuPath-based method for FC size and count analysis. Detection in Adipocyte Tools is also based on rendering dissolved fat areas and is *per se* susceptible to errors. The final benchmark method for comparison of the measurements was therefore Adipocyte Tools with manual correction of faulty detections, which essentially results in detections equivalent to full manual rendering of fat cells (Figure 14).

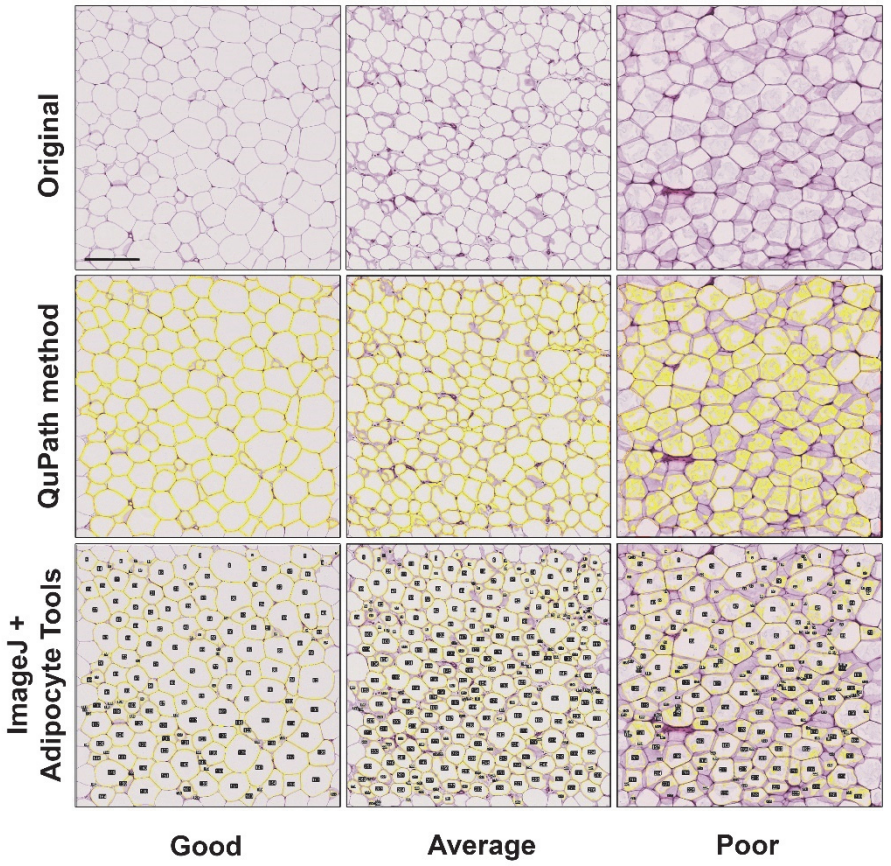

Fig. 12. Comparison of the adipocyte detection with QuPath-based method and ImageJ plugin Adipocyte Tools and visual grading scale good-average-poor. Scale bar 200 µm. Reproduced under the terms of the copyright holders (CC BY) (III).

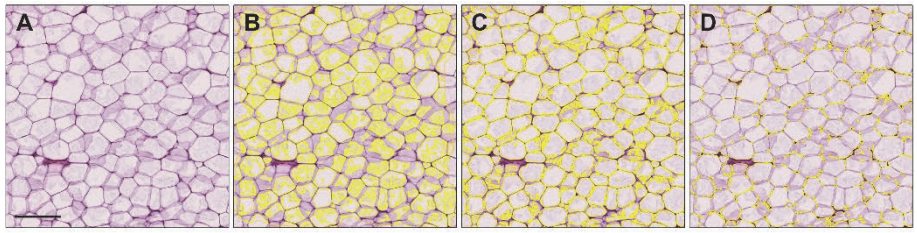

Fig. 13. Alternate pixel classifier training cannot overcome the difficulties with poorly stained samples. Clean areas of dissolved fat are crucial to the method (B-D) since training the classifier to detect spill-over staining may result in falsely conjoined cells (C) or even reversal of rendering (D). Reproduced under the terms of the copyright holders (CC BY) (III).

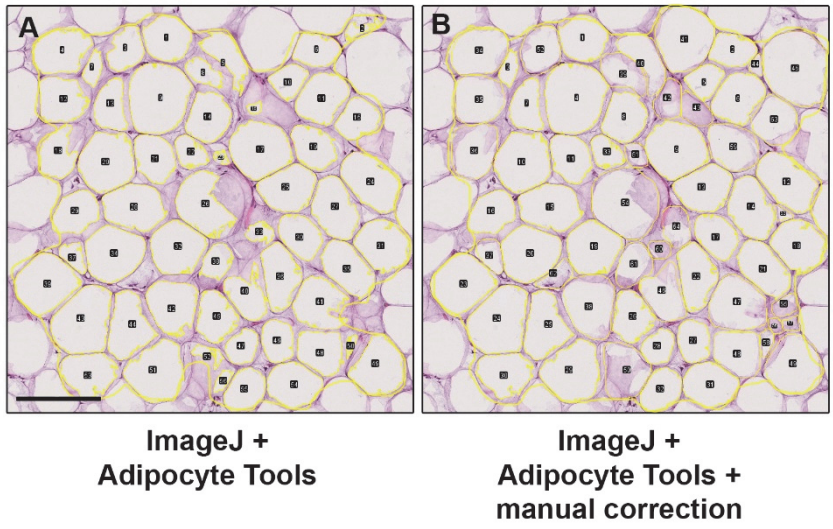

Fig. 14. ImageJ plugin Adipocyte tools is also based on detection of dissolved fat areas and is susceptible to errors (A). However, correcting the rendering of fat cells manually results in detections equivalent to full manual delineation of the adipocytes. Reproduced under the terms of the copyright holders (CC BY) (III).

QuPath-based method versus Adipocyte Tools with manual correction

Adipocyte measurements (count, mean area, mean diameter, and cell density) were obtained from 2 x10E6 µm^2 areas from homogeneous adipocyte areas of 52 samples with average to good staining quality (for example, see rectangle in Figure 16C). The QuPath method found a mean of 304 (SD 60) fat cells versus 327 (SD 67) found with the Adipocyte Tool with manual correction. The mean area measurement was 13.7 µm^2 (0.3%) smaller with QuPath and the mean diameter 0.8 µm (1.1%) smaller than with the benchmark method. Scatter plots, Bland-Altman plot set on the difference and intraclass correlation coefficients (ICC) confirmed the good equivalence of these two methods (Figure 15 and Table 6).

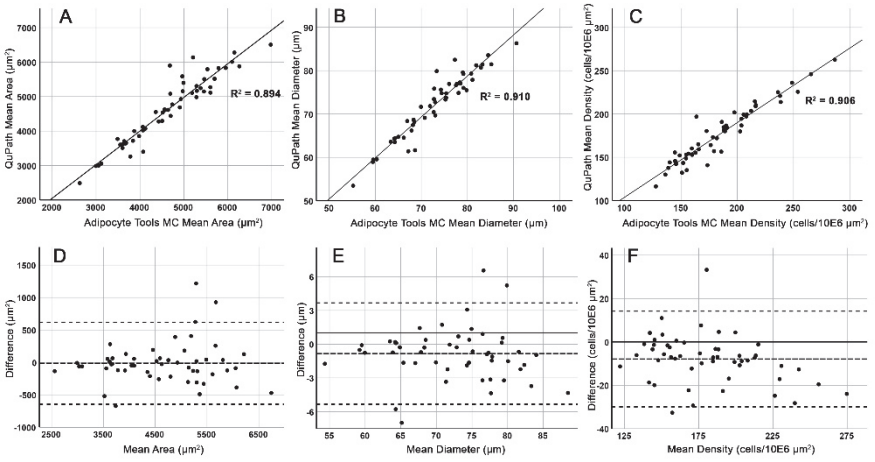

Fig. 15. Measurements obtained using QuPath-based method and benchmark method (Adipocyte Tools with manual correction) show good consistency. A-C: Scatter plots with linear regression for mean area, diameter, and density). D-F: Respective Bland-Altman plots where the middle dashed line is set on mean difference level. Reproduced under the terms of the copyright holders (CC BY) (III).

Table 6. Intraclass Correlation Coefficients and respective 95% Confidence Intervals for average and good samples. Two-way mixed effect model aimed for consistency. Single measures. Reproduced under the terms of the copyright holders (CC BY) (III).

Compared methods	Variable	n	ICC	95% CI
Adipocyte Tools + manual correction vs. QuPath	Count **	52	0.900	0.831 to 0.941
	Area ***	52	0.945	0.906 to 0.968
	Diameter ***	52	0.954	0.921 to 0.973
	Density ***	52	0.945	0.906 to 0.968

F test for all ICC values < .000

ICC = Intraclass Correlation Coefficient

CI = Confidence Interval for ICC

Reliability according to lower CI boundary:

- Good **
- Excellent ***

QuPath-based method in the analysis of large FC areas and whole slides

QuPath handles larger files better than ImageJ. To demonstrate the QuPath-based method developed here, we measured 21 larger adipocyte areas (size range 4.9–17.8 x10E6 μm^2, mean 9.4x10E6 $\mu m^2 \pm$ 3.5x10E6 μm^2) as exemplified in Figure 16B). Table 7B summarizes the results.

Whole-slide analysis is demonstrated in Figure 16D. The attributes of 11,964 found FC are represented in Table 8B along with small area (2x10E6 μm^2) measurements of that section (Table 8A). On an average-powered workstation, attempts to analyze over c. 20x10E6 μm^2 areas sometimes resulted in software freeze, and whole-slide analysis was acquired in pieces.

Table 7. (A) Comparison of ImageJ with Adipocyte Tools plugin and QuPath for adipocyte count, area, diameter, and density according to quality of staining in 40 subjects with BMI > 35 kg/m^2. Adipocyte Tools was used both with and without manual correction. (B) Example of substantially larger areas measured with QuPath method in 21 subjects with BMI > 35 kg/m^2. Reproduced under the terms of the copyright holders (CC BY) (III).

A (2x10E6 µm^2)	n	Count	Mean Area (µm^2)	Mean Diameter (µm)	Mean Density (cells/10E6 µm^2)
ImageJ + Adip. Tools with manual correction (all)	40	315.5 ± 71.7	4827 ± 1290	74.0 ± 9.9	179.6 ± 39.8
- Good	14	324.9 ± 66.4	4906 ± 959	74.8 ± 7.6	182.8 ± 35.0
- Good + Average	34	321.7 ± 68.2	4754 ± 951	73.4 ± 7.6	182.0 ± 34.9
- Poor	14	324.9 ± 66.4	4906 ± 959	74.8 ± 7.6	182.8 ± 35.0
ImageJ + Adip. Tools no manual correction (all)	40	283 ± 63.1	4585 ± 1100	71.5 ± 8.6	176.9 ± 46.6
- Good	14	277.8 ± 54.0	4882 ± 883	74.0 ± 6.9	171.0 ± 29.3
- Good + Average	34	286.1 ± 58.6	4639 ± 950	72.0 ± 7.5	179.4 ± 45.5
- Poor	6	264.8 ± 89.0	4279 ± 1828	68.3 ± 14.0	162.7 ± 54.3
QuPath (all)	40	294.5 ± 63.2	4657 ± 1189	71.8 ± 9.3	172.5 ± 36.6
- Good	14	293.0 ± 58.0	5034 ± 917	74.8 ± 6.7	170.7 ± 31.3
- Average + Good	34	299.2 ± 59.4	4746 ± 1009	72.6 ± 7.7	174.3 ± 33.2
- Poor	6	267.8 ± 82.6	4151 ± 1986	66.7 ± 15.6	162.0 ± 55.1
B (5-18x10E6 µm^2)					
QuPath - large area good + average	21	1613.9	4695 ± 1020	71.8 ± 7.7	175.9 ± 42.6

Values are mean ± SD.

Good, Average and Poor indicate class of section and staining quality

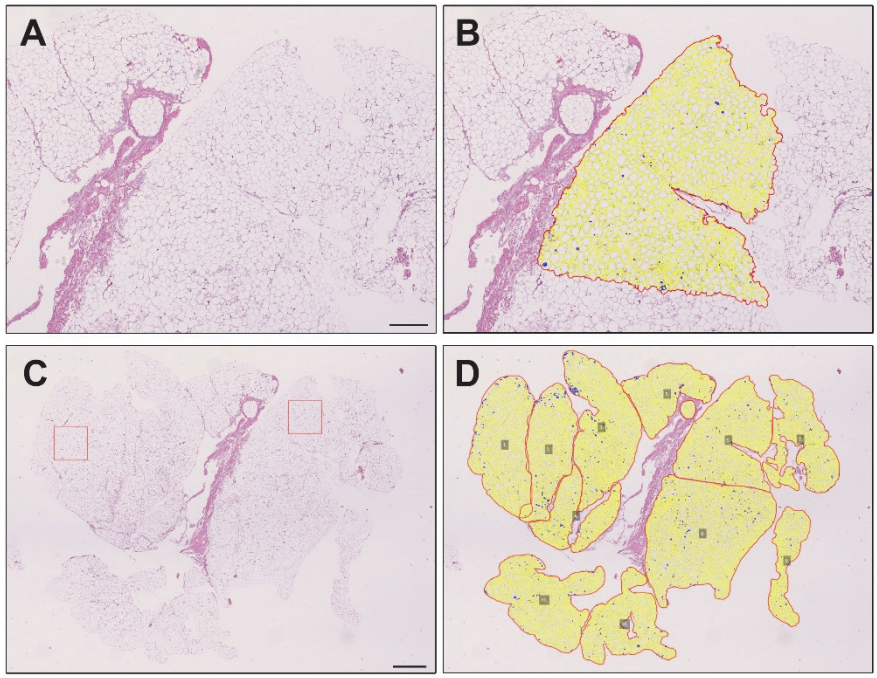

Fig. 16. The QuPath-based method is applicable for analysis of large adipocyte areas as well. A-B: Illustration of the QuPath-based method finding the adipocytes in a larger area (7.1x10E6 µm^2). Scale bar 500 µm. C-D: Analyzing the whole slide requires more effort but can be achieved in pieces on an average-powered workstation (total area 62x10E6 µm^2). Red boxes (10E6 µm^2) demonstrate the areas used for basic analyses with ImageJ + Adipocyte Tools plugin. Scale bar 1,000 µm. Reproduced under the terms of the copyright holders (CC BY) (III).

Table 8. Comparison of ImageJ with Adipocyte Tools plugin (with manual correction) and QuPath protocol for adipocyte count, mean area, mean diameter and density in one sample (Figure 16). Two small areas (A) and large area or whole slide (B) were measured. Reproduced under the terms of the copyright holders (CC BY) (III).

A	Count	Mean Area (μm^2)	Mean Diameter (µm)	Density (cells/10E6 μm^2)
*ImageJ + Adipocyte Tools + manual correction	303	4907 ± 2914	75.2 ± 24.28	172.7
*QuPath	310	4687 ± 2858	73.3 ± 24.31	180.3
B				
QuPath (large area)	1389	4134 ± 3303	68.1 ± 25.1	198.1
QuPath (whole-slide)	11964	4140 ± 4049	67.4 ± 27.1	193.8

Values are mean ± SD for Area and Diameter

* Same two 1000 µm x 1000 µm areas measured with both methods

Comparison of the methods in real-world setting with BMI over 35 kg/m^2 group

To demonstrate the methods and compare the results with those presented in the literature, we used the QuPath method and benchmark method (Adipocyte Tools) to measure FC count, area, diameter, and density for 40 subjects with BMI > 35 kg/m^2. 2x10E6 µm^2 areas with different quality of staining were used. For the QuPath-based method, 21 larger areas from average-good staining pool were also measured. The measurement results (Table 7) indicated that the methods provide comparable results and are also in line with the mean FCS reported for high BMI subjects in whom the BMI-driven increase in mean adipocyte diameter has already plateaued (Laforest et al., 2015). However, with poorly stained sections, both methods provide lower FC measurements without manual correction. It should be noted that the manual correction feature is also applicable in QuPath.

6 Discussion

The main aims of this dissertation were to focus on adipose tissue level inflammatory changes in obesity, and particularly, after bariatric (LRYGB) surgery. Both local and systemic low-grade inflammation have been increasingly recognized as risk factors for myriad obesity-related comorbidities (Hotamisligil, 2006; Johnson et al., 2012; Wellen & Hotamisligil, 2003). Excess fat tissue, especially in visceral fat depots, is susceptible to become dysfunctional as it is confronted by innate inflammatory changes. Dysfunctional fat tissue then contributes to systemic manifestations of distorted adipose tissue biology, such as insulin resistance and T2D (Cottam et al., 2004; Hauner, 2004; Van Kruijsdijk et al., 2009). Macrophage infiltration to adipose tissue is a hallmark of chronic inflammatory state (Weisberg et al., 2003; Xu et al., 2003).

Weight loss, especially bariatric surgery induced weight loss, improves many obesity-related comorbidities, alleviates adipose tissue inflammation and decreases macrophage infiltration to adipose tissue (Cancello et al., 2005; Cummings et al., 2004; Kosteli et al., 2010; Pinkney & Kerrigan, 2004).

In Study I, the knowledge about the behavior of different macrophage populations in SAT after bariatric surgery was deepened and the importance of CSL-associated macrophages and their role in adipose tissue inflammation was highlighted. In Study II, a plausible mechanism for macrophage induced inflammation was proposed. In Study III, a new method for adipocyte size and count analysis, also suitable for analysis of large and whole-slide areas, was formulated and benchmarked against existing methods and literature.

6.1 Discussion of the main results

6.1.1 Weight loss after LRYGB

A relevant mean weight loss was only seen in the surgery group. TWL at 12 months after LRYGB was 21.9%, indicating good average response to the surgery (Corcelles et al., 2016; Grover et al., 2019). Moreover, according to meta-analysis, weight loss may continue for up to 4 post-surgery years after gastric bypass (Chang et al., 2014). Initial T2D associated with suboptimal TWL at 1 year after the surgery, and the results are in line with literature representing T2D as one of the negative

predictive factors for post-surgery weight loss (Al-Khyatt et al., 2017; Campos et al., 2008; Fox et al., 2015; Júnior et al., 2011; Kitamura et al., 2020).

6.1.2 Dynamics of adipose tissue macrophage infiltration after gastric bypass

Study (I) is to date the largest prospective analysis of macrophage population behavior in SAT of obese subjects after LRYGB. The central novel finding in our study was that CLS density was reduced in SAT independently of post-surgery weight loss. Moreover, utilizing whole-slide analysis with machine learning tools provided by QuPath/pixel classifier rather than limited microscopic field views led to the conclusion that at most 15–20% of adipose tissue macrophages reside in CLS; the great majority are found dispersed throughout the tissue as single-cell entities. This contradicts some previous reports suggesting that macrophages are mainly found in CLS (Cinti et al., 2005). Nevertheless, to our knowledge, this is the first study measuring separately and systematically both CLS and dispersed infiltrating macrophages in SAT of obese subjects, not to mention adding the effect of LRYGB to the equation. The CD68 antibody as well as MAC-2 antibody used by Cinti et al. may label some other cell types as well. However, CD68 upregulation is more associated with the proinflammatory phenotype of cells (Chistiakov et al., 2016; Cinti et al., 2005; Di Gregoli et al., 2020). Naturally, using several and combinatory antibodies could enhance the cell specificity of the study.

The data presented in Study I indicate that macrophage reduction in SAT after the surgery occurs especially in CLS as the amount of single-cell CD68-stainging remained unaffected. Moreover, CLS density declined in similar fashion in suboptimal weight loss responders as well. Thus, even suboptimal weight loss responders presumably benefit similarly from the reduction in adipose tissue inflammation as highly inflammatory CLS counts decline. In addition, this suggests that weight loss only is not responsible for CLS clearance and there may be other mechanisms driving the adipocytes' demise and subsequent formation of CLS. For instance, FFA which both recruit macrophages into adipose tissue and decrease in concentration after LRYGB, might be a speculative candidate for triggering CLS formation (Kosteli et al., 2010; Liakh et al., 2022). Furthermore, gut-derived bacteria are not only found in adipose tissue, but may also trigger adipocyte death via micelles or bacteria-derived molecular patterns such as lipopolysaccharides (Hersoug et al., 2018). Bariatric surgery is known to alter the gut microbiota, thus raising the question whether some danger signal of bacteria origin could also drive

the adipocyte death and appearance of CLS (Debédat et al., 2019). In the end, the adipocyte hypertrophy may be a necessary, but not sufficient ingredient in the pyroptosis-related adipocyte death leading to subsequent CLS formation. This view is also supported by the notion that CLS density is higher in visceral fat tissue despite it having generally smaller mean FCS than SAT (Camastra et al., 2017).

In summary, LRYGB, known for a high rate of remission of obesity-related comorbidities, resulted in a decrease of highly inflammatory CLS and the macrophages associated with them in SAT of obese subjects. However, the amount of infiltrating single-cell macrophages was not affected by the surgery. Study I thus emphasize the central role of CLS in inflammation and the necessity of differentiating these two macrophage pools in future studies. In regards of the other listed aims of the dissertation, these macrophage features at baseline in SAT could not provide any prognostic information about the postoperatively achieved weight loss.

6.1.3 NLRP3 inflammasome and Caspase-1 distribution in SAT of obese subjects

In Study II, a detailed distribution of NLRP3 and Caspase-1 in SAT of obese subjects was presented. Both these proteins were found to localize predominantly in CD68 positive macrophages and particularly enriched in CLS. Light staining was also observed in the endothelium of small and sparse vasculature in SAT. The staining pattern obtained with NLRP3 and Caspase-1 immunohistochemistry overlapped with the CD68-staining, thus converging any possible quantification results to those represented in Study I with CD68. Therefore, a tedious and time-consuming quantification process was deemed unnecessary with these antibodies.

NLRP3 and Caspase-1 along with the cytokines (IL-1β, IL-18) produced downstream are associated with low-grade inflammation and metabolic consequences of obesity, such as insulin resistance (Barra et al., 2020; Goossens et al., 2012; Lee et al., 2013; Vandanmagsar et al., 2011; Wani et al., 2021). Again, gastric bypass, known for its beneficial effects against metabolic impairments, may have some of its impact mediated by the NLRP3 inflammasome pathway (Buchwald et al., 2004; Mocanu et al., 2015). Thus, NLRP3 and Caspase-1 reduction in adipose tissue along with a decrease of CLS density after the surgery seem to represent at least one plausible mechanism responsible for the improved inflammatory state after bariatric surgery. In other words, this view highlights the significance of baseline CLS density as a source of inflammation and metabolic

impairments of obesity. After all, the surgery did not affect the amount of dispersed single-cell macrophages.

NLRP3 inflammasome has also been studied in the setting of RYGB vs. sham surgery in rats (Mocanu et al., 2015). Indeed, Mocanu et. al found that NLRP3 activity was dampened in visceral fat, and that related to improved glucose tolerance. However, their results were less clear in SAT. In this context, it should be noted that CLS and macrophage density is generally higher in visceral fat compared to SAT (Alvehus et al., 2010; Camastra et al., 2017). The rat model might therefore lack sensitivity when compared to human tissues. It is also known that visceral fat is more harmful than other deposits and one might expect to see larger magnitude of effect in visceral fat.

NLRP3 and Caspase-1 are associated with programmed cell death pyroptosis which is a pivotal ingredient for CLS formation (Giordano et al., 2013; Shi et al., 2017). CLS formation and lifespan is a process that presumably takes days, perhaps even weeks (Gericke et al., 2015; Lee et al., 2013; Murano et al., 2013). However, the strong association of NLP3 inflammasome with CLS suggests that the formation of CLS might be triggered by danger signals sensed by NLRP3. These include extracellular ATP, FFA or bacteria-derived molecular patterns (Mariathasan et al., 2006; Pétrilli et al., 2007; Shen et al., 2021). Discovering the possible triggers of CLS formation might provide means to interfere with the process and diminish the subsequent inflammatory response.

6.1.4 Adipocyte cell size

In Study I, as expected, LRYGB and the associated weight loss resulted in a shift of FCS towards smaller populations. Subjects with T2D had higher mean FCS. This is in line with the literature (Arner et al., 2010; Monickaraj et al., 2012). However, no significant bivariate correlations were observed with FC attributes and baseline weight or BMI. This may be due to the fact that most subjects participating in the study had BMI > 35 kg/m^2, but the BMI-dependent rise of mean FCS had already plateaued (Laforest et al., 2015). In addition, the distribution of excess weight to different depots was no accounted for in the analysis. The observed weak negative correlation between the baseline CSL density and proportion of only large (70–89 μm) adipocytes remains to be explained. However, the correlation was weak.

6.1.5 A straightforward method for adipocyte size and count analysis using QuPath

In Study III, a simple and fast protocol for adipocyte size and count analysis using free open-source software QuPath was developed and validated. The method was demonstrated with H&E-stained sections but should be applicable to other staining methods as well. The method utilizes only basic functions of QuPath and does not require additional plugins or expertise in script or code-writing. The main benefit of the method is the ability to measure FC attributes from large or even whole-slide areas. In addition, any delineation form of area of interest may be used.

Although QuPath already has inbuilt algorithms for the detection of nuclei and cells, none of them are suitable for adipocytes due to their characteristic features such as absence of nucleus in plane of section and the typical appearance of large cell with absence of staining inside. As with the benchmark software, ImageJ with Adipocyte Tools plugin, QuPath also allows manual correction of detections if necessary. However, when pursuing large areas of up to thousands of fat cells, manual correction quickly becomes an unfeasible option.

The method requires successful processing of the specimen. Suboptimal staining or cutting sections results in difficulties to measure attributes reliably. Fragmentation of samples may provide faulty detections, as also observed by other authors using a script and programming-based approach (Tratwal et al., 2020). Nevertheless, in handling poorly processed specimens the method was not inferior to the benchmark method without manual correction.

Pursuing large adipocyte areas in measuring FC attributes is advocated. The benefits of this include evading sampling biases and decreased accuracy with small samples (Maguire et al., 2020). Demonstration of larger and whole slide areas measured in Study III showed a general tendency of increased size deviation and smaller FCS compared to small areas. This indicates that FCS vary according to their location in tissue, or that fat cells might even form clusters of even size range.

Mean FCS diameter in histological sections seems to plateau around 75–80 µm when BMI exceeds 35 kg/m^2 (Laforest et al., 2015). The measurements obtained in Study III in a subset of subjects over that BMI threshold corresponded well with those presented in the literature.

6.2 Limitations of the thesis

In retrospect, probably the main limitation of the thesis was that only subcutaneous adipose tissue samples were acquired. Visceral, and in particular, mesenteric fat is more metabolically active and has a higher density of CLS (Camastra et al., 2017; Rebuffé-Scrive et al., 1990). However, obtaining paired samples would require surgery and would be both difficult and unethical. Still, visceral adipose tissue samples could have been easily collected for the surgery group at 0 months. In addition, the number of subjects could have been higher, which would have especially facilitated subgroup analysis, and the follow-up time could have been more than 1 year and with more timepoints.

Another obvious limitation is that inflammasome NLRP3-Caspase-1 axis downstream products IL-1β and IL-18 were not measured. This would have strengthened the hypothesis that CLS density is a particularly important factor in inflammation of SAT.

A rather trivial limitation for FCS analysis is that in histology, we always analyze a cross-sectional view of a three-dimensional object.

6.3 Clinical importance

The main clinical and scientific finding of the dissertation is presumably the notion of two different macrophage populations in adipose tissue, of which only the CLS-associated pool responds to LRYGB and might therefore be more important in respect of low-grade inflammation of adipose tissue and its systemic effects. So far, the macrophage infiltration into adipose tissue has largely been treated as a single entity in the scientific literature. Perhaps more attention should be paid to the CLS pool in the future. For instance, it may prove beneficial to identify the exact prerequisites and triggers for CLS formation.

6.4 Future considerations

The importance of obesity research is undeniable and the connection of obesity-related comorbidities and low-grade inflammation is well-established.

With the existing material used in this dissertation it would be possible to further confirm and extend the results obtained so far. For instance, measuring NLRP3 inflammasome downstream products IL-1β ja IL-18 in both adipose tissue and blood samples and comparing those to CLS densities might prove beneficial.

It could also be possible to assess known NLRP3 inflammasome triggers such as lipopolysaccharides of bacterial origin and FFA in the samples. However, as noted above, obtaining paired human samples of visceral adipose tissue is difficult.

7 Conclusions and synopsis

In the present study, we explored macrophage dynamics in obesity and after bariatric surgery (LRYGB). Additionally, we developed a new method for adipocyte size and count analysis using the freely available open-source software QuPath. The following conclusions can be drawn:

1. In obesity, SAT contains two behaviorally distinct macrophage populations: infiltrating single-cell and CLS-associated macrophages (Study I).
2. LRYGB induces a weight-loss independent decrease in CLS-associated macrophages and does not affect the other macrophage population (Study I).
3. Macrophage infiltration or CLS density in SAT does not predict post-surgery weight loss (Study I).
4. NLRP3 inflammasome and Caspase-1 localize predominantly in SAT macrophages and are especially enriched in CLS (Study II).
5. The developed method for adipocyte size and count analysis is valid when compared to alternative methods and results reported in the literature. The developed method can be applied to whole-slide analysis as well (Study III).

In addition to scientific data represented, these findings also appeal to common sense and are intuitively comprehensible. Pyroptosis in CLS closely resembles the inflammation seen in macrophage-induced foreign-body reactions. It seems that body physiology manages the dead adipocytes and leftover lipid droplets somewhat similarly to foreign bodies and inadvertently evokes highly inflammatory CLS as a byproduct. In obesity, adipocyte death rate seems to be elevated, resulting in a constant bombardment of adipose tissue with these “endogenous foreign bodies”.

What else than inflammation could follow?

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Original publications

I Palomäki, VA., Lehenkari, P., Meriläinen, S., Karttunen, TJ., & Koivukangas, V. (2023). Dynamics of adipose tissue macrophage populations after gastric bypass surgery. *Obesity (Silver Spring), 31*(1), 184-191.

II Palomäki, VA., Väyrynen, JP., Koivukangas, V., Meriläinen, S., Karttunen, TJ., & Lehenkari, P. (2023). In human obesity adipose tissue NLRP3 is mainly found in macrophages. *Manuscript.*

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