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Correlation between CRP, Albumin and obesity- a systematic review

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ABSTRACT

Obesity is a chronic condition characterised by an accumulation of body fat. It is rapidly becoming an emerging disease in developed and developing countries due to the increasing westernisation of societies and change in the lifestyle. The aetiology of obesity is multifactorial, with a combination of genetic and environmental factors. There are three levels of obesity management: lifestyle modification (diet, physical activity and behaviour change), pharmacotherapy and bariatric surgery. Bariatric surgery is accepted nowadays as the most effective tool in the treatment and control of morbid obesity. Several studies have shownpre- and post-operative nutritional deficiency in obese patients. Additionally, Obesity is a chronic low grade inflammation state which lead to increase in C-Reactive Protein (CRP) and many nutrient deficiencies such as Serum albumin (SA). SA has been frequently used as an index of protein status and has been shown to correlate with risk for surgical complications and mortality.Little research has linked obesity and hypoalbuminaemia. In this review, we want to see whether there is a relation between morbidly obese patients, hypoalbuminaemia and CRP.

Keywords: *CRP, Hypoalbuminaemia, Inflammation, Obesity, Protein.*

1. Introduction

Obesity is a chronic condition characterised by an accumulation of body fat [1]. It is a non-communicable disease which is gaining increasing importance globally and is a rapidly emerging disease in the developed and developing countries, including Saudi Arabia(SA) [1, 2]. This has prompted the World Health Organisation (WHO) to designate obesity as one of the most important public-health threats [2]. Indeed, obesity is well-recognised to associate with co-morbidities such as cardiovascular complications, metabolic complications and respiratory complications [2].

The aetiology of obesity is multifactorial, including genetic factors, Dietary factors, lifestyle factors and parental factors [1]. In Saudi Arabia (S.A), the socioeconomic status of Saudis has been changed due to the discovery of oil, which led to increase in obesity prevalence among Saudis [3].There are three levels of obesity management: lifestyle modification (diet, physical activity and behaviour change), pharmacotherapy and bariatric surgery [4]. However, many patients do not respond to these therapeutic approaches, requiring more effective intervention. In this context, bariatric surgery is nowadays accepted as the most effective tool in the treatment and control of morbid obesity [5]. Among the main benefits of this intervention, loss and weight maintenance in the long-term and improvement or control of associated diseases stand out, with consequent improvements in the quality of life [5].

Several studies have assessed nutritional status after bariatric operations, detecting reduction in the dietary intake of proteins, vitamins (A, D, B1, B6, folic acid) and minerals (calcium, iron, zinc, copper and magnesium), and nutrient intake often less than 50% the nutritional needs. Diseases such as protein malnutrition and anaemia, among others, frequently occur. Other studies have investigated the presence of nutritional deficiencies prior to surgery, which may be aggravated by the surgical procedure, resulting in more serious postoperative complications [5].Obesity is associated with a chronic state of low-grade inflammation with progressive immune cell infiltration into obese adipose tissue. Immune cell-derived cytokines and adipose tissue-derived adipokines augment adipose tissue inflammation [6]. C- reactive protein (CRP) is a lowgrade chronic inflammation biomarker thatindependently predicts high-risk patients for cardiovascular diseases (CVD). Although many studies showed increased plasma CRP levels in patients with different inflammatory diseases including obesity [7].SA has been frequently used as an index of protein status and has been shown to correlate with risk for surgical complications and mortality.Little research has linked obesity andhypoalbuminaemia. In this research, we want to see whetherthere is a correlation between morbidly obese patients, hypoalbuminaemia and CRP.

2. Obesity

2.1. Definition

Obesity is a chronic condition characterised by an accumulation of body fat [1]. It is often defined simply as a condition of abnormal or excessive fat accumulation in adipose tissue to the extent that health maybe impaired [8]. It is measured by different methods such as body mass index (BMI), waist circumference (WC), waist-hip ratio, skinfold and percent body fat measurement [8]. It is a multifactorial condition that requires the continuous differentiation of new adipocytes throughout life. Members of the peroxisome proliferator-activated receptor (PPARγ) family control the process of adipocyte differentiation from pre-adipocytes[9].

2.2. Obesity complications.

There are deleterious consequences of obesity which include several chronic diseases:

Cardiovascular system complications like congestive cardiac disease, ischaemic heart disease and cerebrovascular disease. Results from both population-based and clinical studies have documented that the adiposity degree of childhood and adolescence are associated with the increase in severity and number of traditional risk factors for CVD, as well as non-traditional risk factors [10]. Hypertension is another cardiovascular complication of obesity, accounting for 65–75% of the human primary (essential) hypertension risk [11].Another complication is related to the endocrine system.

A review showed that the association between obesity and T2DM is well-established across numerous studies in different populations and the epidemics of these two conditions seem to be related [12]. Wild *et al.* found that 171 million is the estimated number of T2DM worldwide in 2000 and hypothesisedthat the trend of T2DM will continuously increase along with a stable obesity prevalence[13].Another study showed that in 3T3-L1 adipocytes, disruption of insulin signalling was shown after recombinant TNF-a chronic treatment and reduction in expression of GLUT-4 mRNA and insulin receptor substrate-1 due to activation of NF-kB kinase-b intracellular inhibitor by TNF-α [14]. On the contrary, partial protection of mice from HFD-induced IR occurred when a whole body gene deletion of TNF-α or TNF receptor 1 (TNFR1) ' its corresponding receptor' are performed [15]Also, Obese patients are prone to dyslipidaemia which consists of increased Free Fatty Acids (FFA) and triglycerides (TG), decreased HDL-C with HDL dysfunction and normal or slightly increased

LDL-C with increased small dense LDL [16]. Obesity also leads to infertility, polycystic ovarian syndrome (PCOS), menstrual irregularities[1]. A study of human genes showed that 21 of obesity genes are associated with human reproduction and infertility [17].

In addition, Respiratory complications like sleep-disorder breathing such as obstructive sleep apnoea syndrome (OSA) and obesity-related respiratory failure. A study shows that sleep-disordered breathing is common in obese patients, with studies estimating the prevalence of OSA as 2–24% of the population [18].An obesity hypoventilation syndrome and asthma study concludedthat asthma is more common in older and heavier patients[19].Furthermore, Renal and genitourinary system complications like urinary incontinence, chronic renal failure, erectile dysfunction hypogonadism and prostate cancer in males, uterine, ovarian, cervical and breast cancer in females, and still birth [1]. Among obese and overweight pregnant women, the stillbirth unadjusted odds ratios were 2.07 and 1.47, respectively,compared to the normal-weight pregnant women [20].Moreover, gastrointestinal system complications like fatty liver disease, gastroesophageal reflux disease (GERD), hernia, gall bladder and colorectal cancers and cholelithiasis are common[1]. The risk of symptomatic cholelithiasis increases with every increase in BMI[21].

Obesity also is associated significantly with certain dermatoses like acanthosis nigricans, striae, acrochordons, and various infections [22].Complications also includemusculoskeletal system complications like low back pain (LBP), disability, osteoarthritis (OA) and hyperuricaemia which lead to gout[23-25]. In a population-based sample of men, high-intensity LBP and/or disability were associated with increased levels of obesity, particularly in those with an emotional disorder [23]. Many results showed that obesity isstrongly associated with a riskof higher knee OA and a 35% increase in the risk of knee OA with a 5 kg/m² increase in BMI [24]. Moreover, the neurological system is affected by carpal tunnel syndrome (CTS) and cerebrovascular disease and other psychological problems like low self-esteem, depression, social stigmatisation and body dysmorphic disorder [1, 26] .Obesity also leads to huge financial and social health complications. A review in USA gave evidence of four economic impact which are direct medical costs, productivity costs, transportation costs, and human capital costs, and suggested total annual economic costs associated with obesity in excess of $215 billion[27].

2.3. Obesity risk factors

There are various risk factors for obesity. Study shows a genetic basis for obesity development. A systematic review pointed to adipokine gene polymorphisms; IL-1β, ADIPOQ, IL-6, and TNF-α increased the risk of obesity [28]. Various gene polymorphisms that affect metabolism, appetite and release of adipocytokines, like adiponectin, lead to obesity. Prader-Willi syndrome and melanocortin receptor mutations are some of the conditions that feature obesity, but only 7% of obese individual have been found to have known single-locus mutations [1]. The expression of genetic characteristics is influenced by different factors that allow weight loss or induce weight gain, such as leptin [29]. Leptin is a protein produced by adipocytes which regulates metabolism, body weight and reproductive function. It decreases with loss of body fat and lead to a positive energy balance state (food intake exceed energy expenditure).

Dietary factors are associated with obesity, like increased fat intake, increased hidden sugar in prepared foods, low consumption of fibreand inadequate vegetable and fruit intake. The daily eating patterns also seemto be associated with weight change[1]. Childhood dietary habits are related to increased adiposity in adolescent[30].

Lifestyle factors are associated with obesity like physical inactivity and sedentary lifestyle which ledto weight gain. A study showeda 3.5 kg decrease in body weight and 18% reduction in the visceral adipose tissue

in a group which exercised for 12 weeks [31].Other lifestyle factors include decrease smoking rates, insufficient sleep [23], endocrine disrupter, regular use of medications that cause weight gain and later age pregnancy. Parental factors like parental feeding practices, availability and accessibility of food to children, parental feeding style and general parenting are factors that affect children's weight [32].

Other factors associated with obesity are menopause, psychological factors [1, 33],endocrine problems like polycystic ovary disease (PCOD) and Cushing's disease[1], andother social stimulito obesity,includingdifferent incomes[1]. Cultural attitudes are considered an obesity influence [1]. For example, pubescent daughters of the wealthy in a part of Nigeria are sent to fattening hutsbefore marriage.

In Saudi Arabia (S.A), the socioeconomic status of Saudis has changed due to the discovery of oil. The increase in obesity prevalence among adolescents between 1988 and 2005 increased by 3.4% to 24.5%, and the trend continues to increase [3]. Saudi lifestyle has become more sedentary, which is a predictor for poor outcomes of health including chronic conditions like heart disease, diabetes and arthritis[34]. A high proportion of Saudi adolescents spent more than two hours daily on screen time, didnot meet the daily guidelines of physical activity, have short sleep duration, consume carbonated drinks and unhealthy snacks anddo not have a daily breakfast, or sufficient milk, vegetables and fruit intake[35-38].Increasedfat consumption, less energy expenditure, eating for pleasure, and a remarkable shift to westernised fast food are all factors leading to obesity in S.A [3, 36].

2.4. Epidemiological trials.

The incidence and prevalence of obesity is increasing worldwide among both genders, all age groups, all educational levels and all ethnic groups due to the consumption of a high-fat diet (HFD) and sedentary lifestyle. The World Health Organisation (WHO) documented that the obesity prevalence has doubled since 1980and it has shown that the level of obesity has reached an epidemic trend worldwide, with 2.3 billion adults classified as overweight or obese by the year 2015[6, 39]. In 2008, 500 million adults were classed as obese among the 1.45 billion overweightadults (BMI > 25 kg/m²) worldwide and in 2010, an estimated 43 million children under the age of 5 years were classed as overweight [40]. This is an alarming and overwhelming situation that needs urgent public health intervention in facing this problem.

In Saudi Arabia, asignificant increase in prevalence of obesity among adolescents, in the period from 1988 to 2005, has been documented [3]. It has been shown by the National Growth Study that the prevalence of obesity in 5-18 year-old children and adolescentsis 11.3%. The prevalence of obesity in females and males was 11.0% and 7.8%, respectively, in the 5-12 year-old group,and 12.1% and 13.8%,respectively, in the 13-18 year-old group[8, 41]. Similar results have been shown by The Arab Teen Life-style Study which included school students aged 14-19 years; here,the prevalence was 14% and 24.1% in females and males, respectively[2].

2.5. Obesity management.

Obesity management includesweight loss, the prevention of weight regain and reducing the risk of disease[4]. There are three levels of obesity management: lifestyle modification (diet, physical activity and behaviour change), pharmacotherapy and bariatric surgery [4].

2.5.1. Modification of lifestyle.

Most certainly, the foundation of obesity care is lifestyle modification. Counselling on choosing a balanced, calorie-controlled diet, engaging in daily physical activity and implementing changes that are practical and sustainable isnecessary for all patients to reduce weight [4]. There are different methods usedto reduce weight such as energy restriction, which is popular and widely promoted, but most of these approaches lead to short-term weight loss success, have little or no impact on the epidemics of obesity and most people return to their initial weight or regain more weight than was initially lost. In the United States, more than two-thirds of adults and two-thirds of women remain obese and overweight [42]. On average, lifestyle modification is effective in achieving a 7-10% weight loss over 6 months when delivered by trained interventionists[4].

Behavioural therapy combined with a low calorie diet is effective both individually and in groups [1]. It involves advice like avoiding situations that lead to overeating, keeping food out of sight and allowing eating at the table only [1]. Eating management practices like eating slowly is also considered under behavioural therapy. Behaviour substitution, like exercising instead of eating when angry, can be done.

2.5.2. Drug therapy

Intensification of treatment beyond lifestyle counselling can be considered for patients who fail to reach their weight loss goal, who have comorbid conditions that would be expected to improve with further weight loss (e.g., diabetes, dyslipidaemia, hypertension), or who regain their weight [4]. Medications for obesity treatment are used to increase the output of energy, decrease intake of energy or decrease nutrient absorption [1]. Methylcellulose is a drug for obesity management which causes a decrease in nutrient absorption. The ineffectiveness of this drug has been found for obesity treatment [1]. Phenteramine is another drug which leads to appetite suppression, but it is only licensed for 3 months use in patients with moderate to severe obesity. The rapid relapse after short-termcourses of this drug has been found along with an added risk of pulmonary hypertension[4]. Orlistat (Xenical) is another drug which decreases the absorption of fat in the intestines. It is only recommended for motivated patients (who have lost over 2.5 kg during the previous month and have 30 kg/m^2 BMI). It is an expensive drug and needs a medical action plan, whichincludes exercise and diet [1].

2.5.3. Surgery

Treating obesity by surgery should be the last solution after a failure of dietary and behavioural modifications and with a BMI over 40 kg/m^2. One of the surgical modalitiesis done by wiring of the jaws together to allow only a liquid diet to be taken in by a straw [1]. Another surgical modality is gastroplasty, which is the most common procedure in developed countries for managing obesity; however, there is a high mortality rate following this procedure [1]. Gastric bypass, vertical gastric banding (VGB) and adjustable silicone gastric banding (ASGB) are other surgical modalities for managing obesity [1].

3. Inflammation and obesity

Inflammation is a local response to the injury of cells that causes increased blood flow, dilatation of the capillary, infiltration of leucocytes and localised production of chemical mediators, which lead to the initiation of toxic agents' elimination and damaged tissue repair [43]. "It is now clear that the termination of inflammation is an active process involving cytokines and other anti-inflammatory mediators, particularly lipids, rather than simply being the switching off of pro-inflammatory pathways" [43].Inflammation is a double-edged sword; it is an important component of immuno-surveillance and host defence;however, a chronic low-grade inflammatory state is a morbidity characteristic of many chronic conditions such as the metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and CVD [43].

3.1. Inflammation associated with obesity

A little more than a decade ago, the first molecular link between inflammation and obesity — TNF-α — was identified when it was discovered that this inflammatory cytokine is overexpressed in the adipose tissues of rodent models of obesity (Table 1). As is the case in mice, TNF-α is overproduced in the adipose as well as muscle tissues of obese humans (Table 2). Thus, particularly in experimental models, it is clear that overproduction of TNF-α in adipose tissue is an important feature of obesity because fat tissue is a significant source of endogenous TNF-a production and TNF-a will induce insulin resistance throughits ability to inhibit intracellular signalling from the insulin receptor[44].

It rapidly became clear, however, that obesity is characterised by a broad inflammatory response and that many inflammatory mediators exhibit patterns of expression and/or impact insulin action in a manner similar to that of TNF-α during obesity [45-47]. Transcriptional profiling studieshave revealed that inflammatory and stress-response genes are among the most abundantly regulated gene sets in adipose tissue of obese animals [48].Obesity-induced IR pathogenesis is critically interfaced by adipose tissue. Adipose tissue was known as a store for inert storage but it is now known as a vital endocrine organ fundamental in systemic lipid and glucose homoeostasis maintenance [49]. Large amounts of adipokines are secreted by this metabolically active organ included leptin and adiponectin [50, 51]. It also maintains energy homoeostasis by regulation of NEFA flux to and from adipocytes [52, 53]. Expansion of adipose tissue leads to an increase secretion and decrease production of pro-inflammatory and anti-inflammatory cytokines, respectively [49, 54]

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Table 1. Obesity and inflammation in mice

Study design	Main result
Measure the IR tyrosine kinase activity in the obese mice and insulin resistance after neutralising TNF-a[55].	) Marked increase in insulin-stimulated auto-phosphorylation of the IR, as well as phosphorylation of insulin receptor substrate 1 (IRS-1) in muscle and fat tissues, restoring them to near control (lean) levels.
Measure the expression of TNF-α gene in the tissue of lean and obese mice [56].	) Elevation of TNF-α mRNA per unit of RNA by five- to ten-fold in obese animals compared with lean controls.

Table 2. Obesity and inflammation in humans

Study design	Main result
Test the expression pattern	) Obese individuals express 2.5-fold more TNF-a mRNA in fat

of TNF-α mRNA in adipose tissues from18 control and 19 obese premenopausal women before and after weight-reduction program[44].	tissue and show increased adipose production of TNF-α protein in comparisonto lean controls.) After a weight-reduction program, a decrease in TNF-a mRNA expression in fat tissueoccurs which leads to an improvement in insulin sensitivity.
Test the TNF expression in 39 lean, obese, and reduced-obese human subjects [57]	) There was a significant increase in adipose TNF mRNA levels with increasing adiposity. In addition, there was a significant decrease in adipose TNF with weight loss.
Quantification of TNF in the muscle biopsy specimens from 15 subjects with various insulin sensitivity. Quantification of TNF in the muscle biopsies cultured for 4 weeks and induced to differentiate into myotubes in 9 human subjects[58].	) TNF expression in the insulin resistant subjects and the diabetic patients was four-fold higher than in the insulin sensitive subjects. .) Cells from diabetic patients expressed three-fold more TNF than cells from non-diabetic subjects.

3.2. Macrophages in obese adipose tissue.

Obesity is associated with a chronic low-grade inflammatory condition combined with immune cell infiltration, mainly macrophages, into obese adipose tissue of mice (Table 3)[48, 59]. Weisberg *et al*. found that 30% of 1304 transcripts in the adipose tissue of mice that correlate to body mass are characteristic of macrophages. An immunohistochemical analysis shows that macrophage-specific marker F4/80 is increased significantly in adipose tissue with a correlation to body mass and adipocyte size [48]. Adipose tissue macrophages (ATM) are considered the predominant source of pro-inflammatory cytokine TNF-α. In adipose tissue, Xu *et al*. found down-regulating effect of rosiglitazone "an insulin sensitising drug" on the expression of macrophage-specific genes which was up-regulated prior to hyper-insulinaemia[59]. In line with these studies, weight loss in humans by diet or surgery leads to reduced infiltration of Adipose Tissue Macrophages (ATM), low-grade inflammation and CCL2/MCP-1 (Table 4)[60, 61]. All of these studies point to the harmful effect of macrophages to the biology of adipose tissue and place it at the forefront of investigations. *In vitro* study shows exacerbation of local inflammation and potentiate IR and T2DM development due to ATM-adipocyte

interactions [62]. Suganami *et al*. demonstrated that the exposure of 3T3-L1 adipocytes to RAW264 macrophage-derived conditions show an increase in IL-6, MCP-1 and the expression of TNF-α mRNA, while incubation of the RAW264 macrophages with adipocyte-conditioned media enhance the expression of IL-6 and TNF-α [40].

Adipose tissue is the largest endocrine organ in the body; along with the ATM, this produces a lot of mediators that lead to a pro-inflammatory response [63]. Adipocytes produce adipokines such as leptin, adiponectin and resistin[64, 65], while macrophages produce large amounts of IL-β; both cell types produce TNF-α and IL-6 [66]. Adipose tissue is also responsible for the uptake of glucose from intracellular sites to the plasma membrane, which is mediated by GLUT4. Down-regulation of GLUT4 and insulin receptor substrate-1 by macrophage-derived pro-inflammatory factors will lead to immune cell-mediated IR [6].

Table 3. Macrophages and obese adipose tissue in mice

Study design	Main result
In vitro studies in different adipose tissues of groups of mice with various adiposity [48].	) Positive correlation between adiposity, body mass and number of macrophages) Positive correlation between M1 macrophages, adipocyte size and body mass.) Adipose tissue macrophage numbers increase in obesity and participate in inflammatory pathways that are activated in adipose tissues of obese individuals.
In vitro studies using multiple tissues of genetic or diet-induced obese mice[59].	) Expression levels of genes in inflammatory pathways are significantly up-regulated in WAT of obese mice.) The expression of inflammation genes is restricted to, or enriched in, macrophages.

Table 4. Macrophages and obese adipose tissue in humans

Study design	Main result
In vivo study of inflammatory markers in 27 severely obese humans after a15-wk lifestyle intervention (hypocaloric diet	Reduction of body weight resulted in:) Increase ininsulin sensitivity.) Increase in plasma adiponectin

and daily exercise) [60].	⁾ Decrease in C-reactive protein, IL-6, IL-8, and monocyte chemoattractant protein-1. ⁾ Reduction in AT inflammation was reduced. ⁾ Decreased expression of macrophage-specific markers (CD14, CD68), IL-6, IL-8, and TNF-α.
In vivo study of subcutaneous WAT of 7 lean and 17 morbidly obesesubjects before and after bypass surgery [61].	⁾ Decrease number of scWAT-infiltrating macrophages and improvement of the inflammatory profile after weight loss.

4. CRP

4.1. Synthesis, metabolism and distribution

CRP is an acute-phase protein and is one of the most sensitive and most recurrent markers of inflammation. CRP is synthesised and excreted primarily by hepatocytes in response to pro-inflammatory cytokines. CRP is present in the serum of healthy individuals in small quantities, and its concentration increases rapidly over the course of inflammation or necrotic processes [67].

4.2. Physiological function

CRP is involved in all stages of the design, remodelling, and rupture of plaque. This increases the influx of inflammatory cells to the walls of the arteries, the expression of adhesion molecules on the surface of endothelial cells, and the synthesis of monocyte chemotactic protein, endothelin-1, plasminogen activator inhibitor-1, while reducing the bioavailability of nitric oxide. It also increases the uptake of LDLs by macrophages and is involved in the activation of complement components. In addition, CRP enhances the formation of blood clots, thereby mediating the remodelling and destruction of plaque [67]. Elevated concentrations of CRP reflect endothelial dysfunction through the deterioration of its anti-inflammatory activity [67]. CRP is correlated with the components of metabolic syndrome: atherogenic dyslipidaemia, obesity, and insulin resistance [67].

4.3. Increase CRP in relation to inflammation

CRP is an acute phase reactant protein which is important against inflammation in non-specific host defence. CRP levels could be raised several folds during infections and trauma, but during low-grade inflammation, only small increases above the baseline can be predicted. High-sensitivity CRP (hs-CRP) is a more sensitive CRP assay which allows the lower level determination of CRP and has been established as an inflammatory marker in a wide range of medical conditions. Different factors has been associated with increased level of hs-CRP such as age, BMI and smoking [68]. Many pilot [69], cross-sectional [7] and population-based [70]studies showed that serum CRP levels may be a good predictor of diseases like CVD and T2DM[71]. These

findings are supported by laboratory and experimental evidences demonstrating that plaque forming is a chronic inflammatory process as well as being a lipid accumulation disease. Surprisingly, CRP was a strong predictor of CVD even after 8 years of initial testing [7]. Besides, low-grade chronic inflammation is an independent predictor of CHD. CRP levels as a biomarker of inflammation have been demonstrated in many prospective studies as an improved method to identify patients at risk of myocardial infarction, stroke, CAD and sudden death (Table 5). Also, a study performed on the relationship between polycystic ovarian syndrome (PCOS) and serum CRP levels showed that plasma CRP levels are significantly higher in patients with PCOS compared to healthy individuals, CRP level increased significantly only in patients with PCOS with BMI ≥ 25 kg/m^2 and BMI and WC affect CRP rising in patients with PCOS [7].

Table 5. CRP and Inflammation

Study design	Main result
In vivo study using 93 Acute Myocardial Infraction (AMI) patients and 201 controlsto investigate the association between serum leptin and AMI and its correlation with IL-6 and hs-CRP [70].	⁃ Higher serum leptin level in AMI patients compared to Non-CVD controls. ⁃ Elevation of IL-6 and hs-CRP in AMI group and leptin correlated positively with IL-6 and hs-CRP.
In vivo study using 718 small-artery occlusion (SAO) patients to investigative the association between hs-CRP levels and outcomes of the patients [72].	⁃ Elevated hs-CRP in patients with SAO is an independent predictor of poor prognosis in younger patients.
In vivo study of 30 young CAD patients measuring the levels of oxidative stress, dyslipidaemia, and high sensitivity-C reactive protein (hs-CRP) [69].	⁃ hs-CRP levels were increased significantly in young CAD patients as compared to controls.
In vivo study of 40 PCOS patients and 30 control to investigate its correlation with CRP [7].	⁃ Higher CRP levels in patients with PCOS. ⁃ Significant increase of CRP level only in patients with PCOS with BMI ≥ 25 kg/m. ⁃ BMI and WC affect CRP rising in patients with PCOS.

4.4. Increase CRP in relation to obesity

Adipose tissue plays an important role in the body's inflammatory processes [67]. Adipocytes are, in fact, the source of pro-inflammatory cytokines, including IL-6, which is one of the most important factors that influences the hepatic production of CRP. Obesity, therefore, contributes to the formation of a pro-inflammatory environment [67]. It has been shown that anthropometric indicators, such as BMI (in kg/m^2) and waist circumference (WC), are correlated with CRP (Table 6). However, the main determinant of serum hs-CRP concentration is not only the amount of body fat but also its distribution. It was shown that adipocyte abdominal fat may have a higher concentration of IL-6 [73] and higher CRP secretion than subcutaneous depots [67]. CRP concentrations are higher in obese patients, especially patients with excess visceral fat, than in patients of normal weight [67].Despite intensive research, the cause of chronic inflammation is not known. Presumably, it is because of the stimulation of the immune system by external factors [high-fat (HF) and high-calorie diets, infections, mental stress, oxidative stress]. However, a special role is attributed to diet [67]. Several studies have shown a significant relation between hsCRP and IL-6 and various dietary factors in humans, suggesting that- the concentrations of inflammatory biomarkers can be modified by diet [74]. Until now, many studies have focused on the relation between individual nutrients and the concentration of inflammatory markers and risk of NCDs, but, recently, it has been demonstrated that the study of dietary patterns can produce more precise results [67].

Table 6. CRP and Obesity

Study design	Main result
Community-based Korean cohort of 9773 humans with hs-CRP ≤ 10 mg/l to evaluated the relationships between hs-CRPand various obesity indices [75].	) Strong correlation betweenfat percentand hs-CRP levels.
In vivo study using 163 elderly people to evaluate the relationships between fasting glucose levels, hs-CRP, BMI and serum retinol and diet [76].	) Significant correlation between hs-CRP, BMI and total calorie intake.
Evaluate the degree of obesity and plasmahs-CRP levels in relation to insulin resistance status among 1438 school children in Taiwan [77].	) Plasma hs-CRP levels are positively related to BMI and insulin levels.

5. Albumin

The human serum proteins albumin (ALB), vitamin D-binding protein (VDB) and α-fetoprotein (AFP) are members of a multigene family. All three proteins,the transport of a broad range of ligands is mediatedin serum. ALB binds amino acids, fatty acids, steroids, metals, glutathione, bilirubin, haematin, prostaglandins,

lysolecithin and pharmaceuticals. AFP binds bilirubin, metals and fatty acids. VDB binds fatty acids, C5a, C5a des-Arg, actin, vitamin D and its metabolites[78]**.**Members of the ALB family have considerable structural similarities [78]. At the primary sequence level of amino acids, homology has been observed, and there are also secondary structure similarities in the presence of a well conserved pattern of Cys residues. Thefamily of ALB genes have organisations with similar exon-intronstructures, and all are located within the region 4qll-q22 in human chromosome 4.Serum albumin is multifunctional, non-glycosylated, negatively-charged [79] and the most characteristic and abundant plasma protein that is synthesised by the mature liver; albumin works as a transporter of different substances and is a basic regulator of colloid osmotic pressure [80]. The albumin is synthesised exclusively in the liver with an approximate amount of 150 mg/kg per day [81], resulting in a concentration of high steady-state in plasma (35–50 g/l in humans). There arestudies which have reported that the level of albumin in plasma is decreased as a result of reduced synthesis of albumin clinical disorders like liver disease [82], inflammatory disease [83], and cancer[84]. Serum albumin is considered a reliable indicator ofthe severity and prognosis of these diseases [80]. Therefore, it is possible that the synthesis of albumin is regulated dramatically and accurately in a wide range of pathophysiological and physiological conditions. It contains three specific domains acting as binding sites for many exogenous and endogenous toxins, drugs and drug metabolites which reflect the antioxidant, anti-inflammatory and scavenging properties of albumin[85].

5.1. Synthesis, metabolism and distribution

Human serum albumin (HSA) possess around 50% of proteins circulating in plasma with concentrations in serum of 35-50 g/L in a healthy individual. The reflection of this level indicates the synthesis, distribution and metabolism of HSA, but not its function [82]. The synthesis of albumin is mainly regulated at the transcriptional level by tissue-specific transcription factors such as C/EBP (CCAAT/enhancer-binding protein) and HNF (hepatocyte nuclear factor)-1 [80]. Many factors down-regulate albumin gene transcription, such as vitamins, cytokines, colloid osmotic pressure and limitation of amino acids [80]. Hepatocytes synthesise HSA (10-15 g/d) and release it into the portal tract [82].

The majority of total body HSA passes into the interstitial space and a minority remains within the bloodstream. Radio-labelled HSA has been injected and shows a trans-capillary escape rate (TCER)of 4.5% per hour [86]. TCER in fenestrated capillaries depends on permeability of capillary wall, hydrostatic and oncotic pressure gradients (liver, pancreas, small intestine, bone marrow) but in non-fenestrated capillaries, HSA passes through to the interstitial space by binds to albondin. This rate of transfer is increased with cationisation, long-chain fatty acid binding and glycosylation of HSA. Lymphatic system returns three quarters of albumin in extravascular space to the intravascular space.The half-life of HSA is approximately 15 d. The majority of HAS degradation occurs in muscle and the skin (the main locations of extravascular HSA), but it also takes place in the kidney and liver [86]. HSA alteration or denaturation result in breaking thisdown into free amino acids by binding to endothelial cell surface receptors, uptake into intracellular vesicles and fusion with lysosomes. The fractional degradation rate (FDR) of HSA is 3.7%,which equals the rate of synthesis in health.

5.2. Physiological function of HAS

5.2.1. Colloidal osmotic pressure (COP)

Maintain colloid oncotic pressure is the HAS classical physiological role, where 80% of the normal plasma oncotic pressure (around 25 mmHg) is maintained by HSA due to its concentration in the blood combined with its high molecular weight[86]. This direct osmotic effect provides 60% of the net negative charge and 40% of the oncotic pressure. The existence of charged residues and the plenty of HSA are factors

important for its role as a physiological buffer. Half of the normal anion gap is HSA responsibility, and as such a decrease inHSA concentration leads to metabolic alkalosis.

5.2.2. Binding function

Regardless of the strong negative charge of HSA, it binds to a wide variety ofnegatively and positively charged compounds, including long-chain fatty acids and divalent cations (but not monovalent) like magnesium and calcium, and hydrophobic organic anions like bilirubin [87]. Some examples of other important biologically compounds bound by albumin are bile acids, a wide variety of drugs, copper, zinc, and also compounds with certain serum binders like vitamin D and thyroxin. The free concentration of compounds is reduced by albumin binding and limits their biologic activity, distribution, and clearance rate. In some compounds, like unconjugated bilirubin, this binding is so avid that controversy exists as to how the liver is able to clear this compound at the observed rate of about 5 mL/minute [88].

5.2.3. Antioxidant activity

More than 50% of the total antioxidants of normal plasma are provided by albumin[89]. The ability to scavenge a wide range of oxygen free radicals including nitric acid and hypochloric acid return to the abundant reduced sulphhydryl groups of albumin. In addition to this ingrained antioxidant activity, albumin also binds to an efficient antioxidant, unconjugated bilirubin. This antioxidant activity is frequently assumed to be the mechanism responsible for the inverse strong correlation between the mortality and morbidity of many disease states and unconjugated bilirubin concentration in plasma.

A wide range of other functional activities are performedby ALB family proteins like maintaining microvascular integrity, metabolic functions, and anticoagulant effects[86]. HSA transport heparin cofactor II and anti-thrombin both inhibit thrombin generation, which increases the anticoagulant activity of natural exogenous heparins and heparinoids. Hyper-aggregation platelet has been linked to hypoalbuminaemia in peritoneal dialysis patients [82], and may contribute to the pro-coagulant tendency seen in acute kidney injury and with chronic liver failure [90]. HSA enhances many immune pathways and may facilitate intracellular protection from oxidative stress and inflammation. In experimental studies, inhibition of tumour necrosis factor-alpha (TNF-α), up-regulation of vascular cell adhesion molecule 1 and activation of nuclear factor-kB are roles of HAS [91]. The stability of endothelial cells is seen by reducing oxidative stress, inflammation dampening and decreasing neutrophil adhesion to endothelial cells are roles of HSA in intravascular space. Vascular integrity could be supported by HSA binding in the sub-endothelium leading to reduced endothelial permeability.

5.3. Structure and ligand binding properties of HSA

HSA is composed of 585 amino acids and has a molecular weight of 66500 Daltons. X-ray crystallography determined the heart-shaped globular structure of HSA with cross-linked cysteine residues and united three domains by 17 disulphide bridges [85, 92], which give HSA strength and also enhance conformational changes in response to ligand binding. There area lot of charged lysine, glutamic acid, arginine and aspartic acid residues with a free tryptophan and cysteine residue, but no carbohydrate moiety[93]. All the three homologous domains (I, II and III) of HSA are constructed from two sub-domains, the A domain with 6 α-helices and the B domain with 4 α-helices[93]. Each domain has a different binding siteproperties, but electron magnetic resonance spectroscopy elucidated nine binding sites for fatty acids [82]. Movement of subdomains to accommodate ligands are allowed by flexible loops made of proline residues. The HSA molecule acts as the transport vehicle for steroid and thyroid hormones, unconjugated bilirubin, fatty acids, and several drugs [94].

5.4. Hypoalbuminaemia in disease

The concentration of HSA depends on various factors like: hepatocyte function, hepatic synthesis, ingestion and absorption of protein subtracts, abnormal albumin loss (kidney disease, eclampsia and Protein-losing enteropathy), burns, high catabolism infection and distribution volume affected by hydration status [95].

HSA synthesis, degradation and distribution can be changed by diseases. Many cohort studieshave shownthat hypoalbuminaemia is common in inflammatory disorders which can be explained by inflammatory cytokines which decrease the synthesis of constitutive proteins, such as serum albumin, and increase its degradation. They also promote capillary permeability and leakage of serum albumin into the extravascular space. Because CRP is affected by increased interleukin-6 during acute inflammation, a decrease in serum albumin occurs with increased CRP (Table 7). In malabsorption and malnutrition, the decrease in the synthesis of HSA occurs due to a deficiency of amino acids [82].

In hepatocyte loss or dysfunction, like in advanced liver disease, there is a decreased synthesis of HSA. In Child-Pugh-Turcotte score, HSA is one of its components [82], in patients with cirrhosis a disease severity score is widely used, although HSA is not a component of the more recent model for end-stage liver disease (MELD) [96]. Increased endothelial permeability lead to an increase in the shift of HSA into the interstitial space. Sever sepsis hallmark is increased capillary leakage and vasodilation, and lead to multiple organ dysfunction [97]. Many pro-inflammatory and vasoactive mediators produce loss of endothelial integrity and vasodilation in sepsis, such as TNF-α, endotoxins, IL-1, IL-6, nitric oxide and prostacyclin, leading to HSA TCER increasing three-fold[82]. This HSA leakage into the interstitial space is not associated with a concomitant increase in lymphatic return into the intravascular compartment; rather there is increased sequestration in the non-exchangeable sites in the body. After a bolus, plasma HSA falls faster of 20% HSA in patients with sepsis than with healthy volunteers[98].

Furthermore, a reduction in the transcription of HSA mRNA occurs in the context of the acute phase response, mediated by TNF-α and IL-6.In hospitalized patients, acute hypoalbuminaemia is commonly due to decreased synthesis due to malnutrition, acute organ dysfunction and increased trans-capillary escape due to increased endothelial permeability secondary to systemic inflammation[82]. This is noticeable in patients who are chronically hypo-albuminaemic from protein losing nephropathy and enteropathies, chronic malnourishment and cirrhosis of the liver [82]. In geriatric patients, hypoalbuminaemia could be physiologic, as there is 20% less serum albumin in individuals above 70 years old. In this group of patients, levels more than 20% under standard may indicate protein malnutrition and hyper-catabolism, leading to extended lengths of stay, more expensive treatments and implying risks for other kinds of clinical complications [95].

Table 7. Hypoalbuminaemia and inflammation

Study design	Maim results.
Retrospective Study of 37 patients who underwent elective open colorectal surgery to see the correlations between preoperative CRP and serum albumin on various postoperative	) Significant correlations were betweenpreoperative CRP and serum albumin.

days (POD) [99].	
Cohort study of 3430 Chronic Renal Insufficiency participants to examined the association of inflammatory markers and serum albumin with progression of CKD [100].	⁾ Elevated plasma levels of fibrinogen and TNF-α and decreased serum albumin are associated with rapid loss of kidney function.
Large cohort of patients referred for nutritional screen and patients with critical illness to examine the relationships between plasma zinc, selenium and the systemic inflammatory response [101].	⁾ Plasma zinc and selenium was associated with both CRP and albumin.
Two cohorts of patients referred for nutritional assessment and patients with critical illness to examine the relationship between plasma 25(OH)D, CRP and albumin concentrations [102].	⁾ Plasma concentrations of 25(OH) D were independently associated with both CRP and albumin and consistent with the systemic inflammatory response.
Cohort study of 12 patients with gastrointestinal cancer and an inflammatory response compared to a control group andto examine the changes in micronutrient Concentrations following anti-inflammatory treatment [103].	⁾ Cancer group had significantly higher CRP concentrations. ⁾ Concentrations of vitamin, antioxidants and trace elements (and carrier proteins) were significantly lower, except copper (ceruloplasmin) which was significantly higher.

5.5. Hypoalbuminaemia and obesity

Obesity is considered a risk factor for several nutrient deficiencies, including lower levels of anti-oxidants and certain fat-soluble vitamins [104]. A cohort study including 77,785 patientsshowed that patients with morbid obesity are more likely to be malnourished than patients who are not obese [83]. Another two cohort studies show that hypoalbuminaemia is associated with high BMIbecause obesity is a state of

inflammation and thus hypoalbuminaemia might reflect the higher inflammatoryburden among those who are obese rather than nutritional status alone (Table 8).

Recent cohort studies of extremely obese adults undergoing bariatric surgery have been found to have a wide range of nutritional deficienciesbefore the surgery. It is not completely known what is the reason behind these nutritional deficiencies in overweight and obese individuals, but one of the important reasons is the higher intake of processed foods with high calories which contain poor nutritional quality, especially in highly developed countries in which there are plenty of comparatively energy-dense, cheap, but nutrient-poor foods. American adults and children consumea high percentage of low nutrient-density food which comprises almost about 27–30% of the daily caloric intake, with contributions of about 18–24% for sweeteners and desserts in total[105, 106]. Unprocessed nutrient-dense foods contribute the bulk of vitamins and minerals obtained from a non-supplemented diet such as dairy products, fruits and vegetables, whole grains, protein sources, nuts and legumes, and fish. Proportionately, as the intake of unprocessed, nutrient-dense foods decreases the intake of nutrient-poor food increases[105]. Higher fat diets (>30% of total caloric intake) are associated with decreased intake of vitamins A, C and folate [107]. Increased consumption of sweetened beverages is also associated with lower intake of milk, and therefore calcium and fortified vitamin D3 [108]. In the case of vitamin D3, additional risk factors for deficiency may include reduced physical activity leading to decreased sun exposure, increased storage in excess adipose tissue, as well as ethnicity and skin tone [109].

Table 8. Hypoalbuminaemia and obesity

Study design	Main results
In vivo study in 2853 adult with CKD to examined the associations between BMI and WC with various CKD complications [110].	) Correlation between BMI and WCwith hs-CRP level and hypoalbuminaemia.
Analysed 115 women undergoing evaluation for bariatric surgery[111].	) Deficiencies were found in 6.1% of the subjects for albumin, 21.7% for prealbumin.

5.6. Complication of hypoalbuminaemia

HSA has been usually used as an index of protein status and has been shown to correlate with risk for surgical complications and mortality. Protein plays an important role in surgical recovery by facilitating wound healing and immune-competence. Protein deficiency (PD) increase the risk of surgical complications [112]. A cohort study, which included 77,785 patients, shows that patients with low serum albumin were more likely to have a superficial surgical site infection, deep surgical site infection, organ space surgical site infection, pneumonia, progressive renal insufficiency, acute renal failure, cardiac arrest requiring cardiopulmonary resuscitation, septic shock and more likely to require blood transfusion. In addition, any infection and any major complication were more prevalent among patients with low serum albumin [83].

Another study used The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) regarding patients undergoing primary TJA to determine associations between preoperative hypoalbuminaemia and several specific postoperative complications. The study shows that

hypoalbuminaemia was independently associated with age strata, female sex, BMI strata, diabetes mellitus, dyspnoea on exertion, end-stage renal disease, chronic obstructive pulmonary disease, current smoker status, and anaemia. Patients with hypoalbuminaemia had a higher risk for SSI and pneumonia, longer mean postoperative length of stay and higher rate of unplanned readmission [113]. The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) is a prospective surgical registry that samples patients from communitiesand academic centres nationwide. The program prospectively identifies patients undergoing major surgical procedures and tracks them for 30 days for the development of postoperative complications. The program also prospectively collects preoperative laboratory data, including preoperative serum albumin concentration.

6. Future trends in reducing inflammation associated with obesity

Besides controlling weight, efficient amelioration of inflammation associated with obesity is an important factor in the management of obesity. A big variety of phytochemicals or bioactive components in foods and functional foods have become common and have been considered an alternative or complementary therapies for chronic diseases treatment and/or management because they are safer, more effective and affordable [114-116]. Additionally, it is reported that many alternative and complementary exotic herbs, fruits, spices and dietary supplements are used widely in obesity, diabetes and metabolic syndrome treatment/prevention in combined with the standard prescribeddrugs [116, 117]. The purified bioactive compounds and/or whole extract from medicinal foods have many targets to improve these health illnesses and its complications, hence their healthcare burden.

Phytochemicals (such as polyphenols, saponins, phytate, triterpenoid and others) contribute to different pharmacological and biological activities including anti-inflammatory, cardiovascular, hypotensive, hypoglycaemic, anti-microbial,among others [117, 118].*In vitro* studyon the effect of *Tetrapleura tetraptera* extracts (HET) "which have phytochemical composition" on obesity and T2DM rats showed that HET reduced gain of weight, plasma insulin levels and fasting blood glucose, homeostasis model assessment of insulin resistance (HOMA-IR), hypertension, alleviated obesity and T2DM are associated with oxidative stress in rats. Additionally, after HET administration, attenuation of tissue steatosis and liver injury, and a significant hypolipidaemic property was observed. Down regulation of CRP, IL-6, TNF-α, leptin and an increase in adiponectin are further demonstrated by HET [119]and work as anti-inflammatory, antioxidant, and further act in Manchester, antithrombotic and lead to inhibition of platelet aggregation, improvement in endothelial function, and mechanisms that are not mutually exclusive. For that, polyphenols have protective roles in the cardiovascular system [120]. Polyphenols can also suppress adipogenesis and obesity by targeting insulin receptor [121].

Plant based foods such as, Whole-grain (WG) consumption plays a role in body management of weight and digestive health and lowers the risk of chronic diseases like diabetes, cardiovascular disease, and cancer [122]. A study shows, after 8 weeks of WG consumption compared to refined wheat consumption, a concomitant reduction in plasma TNF-α and ,after 4 weeks, increased interleukin (IL)-10 [122]. Another in vitro study using diabetic rats showed improvement in inflammatory biomarkers in the rats fed with riceberry compared to rats fed with fibre[115].

7. Conclusion

Obesity is a chronic condition characterised by an accumulation of body fat. It is rapidly becoming an emerging disease. The aetiology of obesity is multifactorial. Bariatric surgery is accepted nowadays as the most effective tool in the treatment and control of morbid obesity. The presence of high CRP and hypoalbuminaemia

in obese patients lead to various post-operative complications.Correction of CRP and albumin levels is important to avoid post-operative complications. Studies should be carried to see if there is a correlation between CRP, albumin and obesity.Little research has linked CRP, obesity and hypoalbuminaemia. In this review, we want to see if there is a relation.

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