Review

Neurogenic obesity and systemic inflammation following spinal cord injury: A review

Gary J. Farkas , David R. Gater

Department of Physical Medicine and Rehabilitation, Penn State College of Medicine, Hershey, Pennsylvania, USA

Content: Spinal Cord Injury (SCI) results in physiological changes that markedly reduces whole-body metabolism, resulting in neurogenic obesity via adipose tissue accumulation. Adipose tissue has been implicated in the release of proinflammatory adipokines that lead to chronic, systemic inflammation, and evidence suggests these adipokines contribute to the pathogenesis of metabolic diseases that often accompany obesity. In this review, we propose the concept of neurogenic obesity through paralysis-induced adiposity as the primary source of systemic inflammation and metabolic dysfunction reported in chronic SCI. We also briefly discuss how exercise in SCI can attenuate the negative consequences of obesity-induced inflammation and its comorbidities.

Methods: A MEDLINE, PubMed, Google Scholar, and ClinicalKey search was performed using the following search terms: obesity, adiposity, adipose tissue, proinflammatory adipokines, proinflammatory cytokines, metabolic dysfunction, exercise, physical activity, and spinal cord injury. All papers identified were full-text, English language papers. The reference list of identified papers was also searched for additional papers.

Results: Research suggests that obesity in SCI results in a state of chronic, systemic inflammation primarily through proinflammatory adipokines secreted from excess adipose tissue. The reduction of adipose tissue through the use of diet and exercise demonstrates promise to combat neurogenic obesity, inflammation, and cardiometabolic dysfunction in SCI.

Conclusion: Proinflammatory adipokines may serve as biomarkers for the development of obesity-related complication in SCI. Mechanistic and interventional studies on neurogenic obesity-induced inflammation in chronic SCI are warranted.

KEYWORDS: Neurogenic obesity, Adipose tissue, Inflammation, Adipokines, Spinal cord injury

Introduction

Spinal cord injury (SCI) is a medical condition where neurological dysfunction leads to psychological, socioeconomic, and functional limitations. As a consequence of the injury, the sympathetic nervous system and sensory and motor pathways of the spinal cord become interrupted leading to altered physiological responses and skeletal muscle paralysis below the level of injury (LOI).¹ This puts those individuals with SCI at greater risk for body composition alterations that often result in a state of obesity and cardiometabolic dysfunction.²

Obesity is a metabolic disorder marked by excess accumulation of adipose tissue resulting from an imbalance of energy intake and expenditure.³ The condition is an established risk factor for cardiovascular disease, type

2 diabetes mellitus, dyslipidemia, and hypertension, and in recent years has been described as a systemic inflammatory condition characterized by chronic, low-grade inflammation.^{4,5} Obesity is at epidemic proportions in SCI such that the prevalence of obesity is > 66%,^{2,3} but current literature largely fails to attribute adiposity as the source of systemic inflammation in this population.^{2,3,6–13}

Recent reviews associate systemic inflammation following SCI with central nervous system inflammation, but fail to identify the source of the systemic inflammation.^{14–17} Conversely, a growing body of literature implicates proinflammatory adipokines/cytokines secreted directly from adipose tissue as the primary source of systemic inflammation in the nondisabled and individuals with *chronic* SCI (i.e. ≥ 1 year post injury).^{18–22} In this review, we propose the concept of neurogenic obesity to explain the systemic inflammatory milieu associated with chronic SCI. Briefly, SCI causes an obligatory sarcopenia, anabolic deficiency and

Correspondence to: Gary J. Farkas Department of Physical Medicine and Rehabilitation, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, 500 University Drive, P.O. Box 850, Mail Code R120, Hershey, Pennsylvania 17033-0850, USA; Phone: 717-531-0003, x284930, 717-531-0354. Email: gfarkas@pennstatehealth.psu.edu

sympathetic nervous system blunting that markedly reduce whole-body metabolism, resulting in adipose tissue accumulation and neurogenic obesity at nearly twice the rate as non-SCI individuals.³ We also briefly discuss how forms of physical activity in the SCI population can attenuate the negative consequences of obesity and its comorbidities. We aim to summarize some of the most notable research in adipose tissue-derived inflammatory markers using research from both nondisabled and SCI populations with emphasis on markers previously investigated in SCI-induced obesity.

Neurogenic obesity and obesity assessment after spinal cord injury

Obesity has been traditionally defined as an excessive accumulation of whole-body fat marked by percent body fat > 22% in men and > 35% in women.³ However, in the 1990s the World Health Organization²³ defined obesity as an increasing body mass index (BMI) calculated as weight in kilograms divided by height in meters squared. BMI has been widely used for epidemiological studies, however, the classification system is inappropriate for specific populations as it does not account for race, gender, and age, as well as body composition.^{24,25}

BMI also only serves as a surrogate maker for body fat and does not yield a precise measure of body composition, such as fat free mass (FFM) and fat mass (FM), nor the distribution of FM (i.e. android vs. gynoid or subcutaneous vs. visceral fat). This is of concern in populations that experience extreme sarcopenia as a result of disability or injury, such as those with SCI. To date most of the current literature fails to adequately report how changes in body composition in SCI relate to altered lipid, carbohydrate, and vascular profiles in SCI.² These studies typically examine the effects of decreased physical activity, imbalances in energy intake and energy expenditure, and altered catabolic and anabolic hormones with little attention given to the milieu of adipose tissue-derived inflammatory markers that are thought to lead to systemic complications.

Within the first year following SCI there is reduction of anabolic hormones, obligatory sarcopenia, loss of bone mineral content, and an increase in FM. Moreover, these changes are associated with a profound reduction in energy expenditure, resulting positive energy balance manifesting as obesity (Figure 1). Both incomplete and complete injuries experience rapid muscle atrophy through a loss of contractile proteins a few weeks after

Figure 1. Proposed mechanism of proinflammatory adipokines in obesity and metabolic dysfunction following spinal cord injury. **Color Legend:** Blue, anti-inflammatory adipokines; Brown, dyslipidemia; Green, vascular dysfunction and hypertension; Purple, insulin resistance/type 2 diabetes mellitus; Red, proinflammatory adipokines. **Legend:** AIA, anti-inflammatory adipokines; CRP, high sensitivity-c reactive protein; HDL-C, high density lipoprotein-cholesterol; ICAM-1, intracellular adhesion molecule-1; IL-6, interleukin-6; LDL-C, low density lipoprotein-cholesterol; MCP-1, monocyte chemoattractant protein-1; NEFA, non-esterified fatty acids; PAI-1, plasminogen activator inhibitor-1; SCI, spinal cord injury; TG, triglycerides; TNF α , tumor necrosis factor- α ; VCAM-1, vascular cellular adhesion molecule-1; VLDL-C, very low density lipoprotein-cholesterol.

Table 1 Summary of important proinflammatory adipokines elevated in obesity and obesity-related diseases (adapted and updated from Balistreri *et al.*,⁹⁶ Nakamura *et al.*,⁹⁷ and Ouchi *et al.*⁹⁸).

Adipokine	Proposed Mechanism of action	1° release source from AT	2° release source from AT	SCI literature	Role in obesity and metabolic dysfunction	Role of physical activity	Human vs. animal
TNF α	Upregulates SOCS3 which prevents PI3K-PKB cascade in muscle and AT; Upregulates NF- κ B and ERK to stimulate lipolysis	Macrophages in VAT	Adipocytes in VAT (lesser extent in SAT), lymphocytes	FES over 10 weeks reduces TNF α	Elevated in obesity; alters glucose and insulin metabolism to promote insulin resistance; promotes inflammation (directly stimulates CRP)	↓ TNF α expression and helps restore metabolic homeostasis	Human: ↑ with obesity, correlates with BMI and other measures of obesity Animal: ↑ with obesity, inhibition leads to ↑ insulin signaling in muscle and AT
IL-6	Upregulates SOCS3 which prevents PI3K-PKB cascade in muscle and AT; Upregulates STAT3 which stimulates lipolysis	Macrophages in VAT	Adipocytes, preadipocytes, skeletal muscle, endothelial cells, macrophages	↑ vs. nondisabled control in obesity, correlate with vascular inflammation and hs-CRP	Alters lipid metabolism, inhibits glucose uptake to promote insulin resistance, promotes inflammation (↑ hs-CRP) and hypertension, marker for heart attack	↓ IL-6 expression and helps restore metabolic homeostasis	Humans: Correlates to BMI, fat mass, and insulin resistance Animals: similar to humans
PAI-1	Inhibits tissue type plasminogen activator and urokinase-type plasminogen activator	Adipocytes, Macrophages in VAT	Vascular endothelial cells, preadipocytes	Does not ↓ with exercise, correlates with abdominal sagittal diameter	Contributes to atherosclerosis; inhibits fibrinolysis	Variable, however PAI-1 does not ↓ in SCI.	Humans: ↑ obesity and type 2 diabetes mellitus, correlates with VAT Animals: varies
MCP-1	Transcription factor inhibitor of differentiation 3; PKC pathway; TNF α ↑ expression	Adipocytes	Macrophages, endothelial cells	No SCI obesity research	↑ insulin resistance, monocyte recruitment to AT, promotes inflammation and secretion of TNF α and IL-6	Reduces MCP-1 expression and monocyte recruitment to AT	Humans: ↑ in obesity and type 2 diabetes mellitus Animal: ↑ in obesity Both: monocyte recruitment
Resistin	Overall poorly understood in humans, ↓ AMPK, insulin receptors, IRS-1 and 2, ↓ activation of PI3K-AKT/Protein kinase B pathway in preadipocytes and adipocytes; leads to; ↑ SOCS3	Adipocytes (rodents), Macrophages and monocytes (humans)	Skeletal muscle, preadipocytes, and adipocytes (humans)	No SCI obesity research	Promotes insulin resistance in rodents by inhibiting glucose-stimulated insulin secretion; marker for atherosclerosis, heart failure, stroke, heart attack; alters glucose metabolism; promotes inflammation	Reduces resistin expression	Humans: Correlates to adipose tissue and BMI, secreted from a number of tissues, ↑ obesity, ↑ inflammation Rodents: mainly secrete from adipocytes to promote insulin resistance

Continued

Table 1. Continued

Adipokine	Proposed Mechanism of action	1° release source from AT	2° release source from AT	SCI literature	Role in obesity and metabolic dysfunction	Role of physical activity	Human vs. animal
Chemerin	↑ STAT3 to ↑ lipolysis	Adipocytes	Hepatocytes, placenta	No SCI obesity research	Alters glucose and lipid metabolism, alters adipocyte hyperplasia and hypertrophy	Reduces chemerin expression ^{99,100}	Human: correlates with AT and glucose and lipid metabolism, BMI Animal: similar to humans ¹⁰¹

Alphabetical order: ↓, decrease; ↑, increase; AT, adipose tissue; AMPK, adenosine monophosphate-activated protein kinase; BMI, Body mass index; ERK, extracellular signal regulated kinase; hs-CRP, high-sensitivity c-reactive protein; IL-6, interleukin-6; IRS-1 & 2, insulin receptor substrate 1 and 2; NF-κB, nuclear factor kappa-beta; MCP-1, monocyte chemoattractant protein-1; PI3-PKB, Phosphatidylinositol 3-kinase protein kinase B; PKC, Protein Kinase C; PAI-1, plasminogen activator inhibitor-1; SAT, Subcutaneous adipose tissue; SOCS3, Suppressor of cytokine signaling 3; STAT3, Signal transducer and activator of transcription 3; TNFα, tumor necrosis factor-α; VAT, visceral adipose tissue

the injury with a continued reduction up to a year following the injury,^{26–28} which is worsened by greater time since injury, injury completeness, and LOI.^{2,13} Coincident with skeletal muscle atrophy there is a significant loss of bone mineral due to mechanical unloading, anabolic insufficiency, sympathetic nervous system dysfunction, and loss of neurotrophic influences. This increases rates for osteoporosis and fracture below the LOI.^{29–31} Such drastic loss of metabolic tissue results in commensurate loss in energy expenditure, by as much as 54% in persons with tetraplegia, which is rarely matched by a similar change in energy intake, such that adipose tissue accumulates.³² Greater volumes of adipose tissue in both subcutaneous and visceral depots have been reported in SCI and have negatively correlated with percent FFM when compared to the nondisabled population.^{10,11} Those with SCI had nearly a 30% increase in visceral adipose tissue (VAT) volume for every centimeter increase in waist circumference and a similar 20% increase in VAT volume for every unit increase in BMI.¹⁰ This adipose tissue depot has been shown to negatively influence metabolic profiles in the nondisabled and SCI populations.^{2,11} A ratio of VAT to subcutaneous adipose tissue (SAT) greater than 0.40 is suggested to be a risk factor for developing metabolic complications following SCI; those with SCI have a ratio of 0.70.^{2,11} Collectively, these alterations in body composition are thought to put those individuals with SCI at greater risk for cardiometabolic dysfunction.

Pathophysiology of adipose tissue

Adipose tissue is composed of adipocytes which store lipids as triglycerides, and the stromal vascular fraction that contains a variety of cell types such as preadipocytes, smooth muscle and endothelial cells, fibroblasts, lymphocytes, macrophages, and leukocytes. Adipose tissue, specifically the adipocyte, is no longer considered exclusively a storage depot for energy, but has been identified as a secretory organ releasing a host of signaling molecules, termed adipokines (Table 1).³³ These adipokines influence the composition and physiology of adipose tissue through autocrine, paracrine, and endocrine actions which in turn influence whole-body metabolism.^{5,34,35} Currently, adipokines are thought to be involved in the pathogenesis of obesity and obesity-related disorders by activating intracellular stress signaling pathways that interfere with normal cellular metabolism in both human and animal models.^{22,36}

It is well documented that with increasing amounts of adipose tissue there is an alteration in adipokine profiles, as well as the infiltration of macrophages (due to the adipokines) which express many of the same adipokines

as the adipocytes.^{37–39} Many adipokines mediate inflammation and alter physiological function through proinflammatory mechanisms (Figure 1).³⁶ These proinflammatory adipokines negatively influence carbohydrate and lipid metabolism by stimulating the secretion of non-esterified fatty acids (NEFA) from hypertrophic visceral adipocytes, even in the presence of rising insulin levels. Circulating NEFA released from VAT enter the portal circulation and consequently lead to the elevated production of low-density lipoprotein-cholesterol (LDL-C) and very low-density lipoprotein-cholesterol from the liver and a decrease in the production of high-density lipoprotein-cholesterol (HDL-C), thereby contributing to atherosclerotic risk.³ In addition, these NEFAs are deposited into skeletal muscle and the liver preventing the intracellular transport of plasma glucose thereby contributing to a state of insulin resistance (Figure 1).⁴⁰ This pathophysiological characteristic of adipose tissue consequently is thought to contribute to the chronic, systemic inflammatory state and associated comorbidities that often accompany obesity as observed in both nondisabled and SCI individuals.^{19,41,42}

Proinflammatory adipokines

1. Tumor necrosis factor- α

Tumor necrosis factor- α (TNF α) is a potent inflammatory molecule of 157 amino acid subunits that is involved in a number of acute and chronic inflammatory processes, such as favoring a host response and contributing to insulin resistance.^{43,44} The adipokine is dependent on the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and p38 mitogen-activated protein (MAP) kinase pathways in mature adipocytes.^{45,46} Macrophages in the stromal vascular fraction of adipose tissue secrete the majority of TNF α ,^{39,45} however, adipocytes have been implicated as secreting larger amounts of the adipokine.⁴⁶

TNF α was the first discovered adipokine implicated in the link between obesity, type 2 diabetes mellitus, insulin resistance, and inflammation.^{45,47} This adipokine may be the initial trigger in systemic inflammation and may subsequently prolong the inflammatory state by further triggering its release from adipose tissue.⁴⁸ This proinflammatory adipokine is thought to promote insulin resistance through the upregulation of suppressor of cytokine signaling-3 (SOCS3). This inhibits the phosphorylation of the insulin receptor substrate 1 (IRS-1) and subsequently the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (PKB, Akt) signaling cascade in muscle and adipose tissue (Figure 1).^{3,49,50} In addition, TNF α downregulates GLUT4 gene

transcription and translocation in both tissues.⁵¹ TNF α is also thought to be able to induce insulin resistance by negatively influencing both the differentiation and lipid metabolism of adipocytes through the activation of NF- κ B and extracellular signaling regulated kinase, as well as reducing the secretion of anti-inflammatory adipokines. This leads to an increased lipolytic state with the infiltration of NEFA into skeletal muscle (Figure 1).⁵² Intramuscular fat is therefore increased, as noted in SCI.^{2,27}

The concentration of TNF α in adipose tissue and plasma is higher in that of obese individuals, such that with the loss of adipose tissue these levels decrease.⁵³ When examining obese individuals with type 2 diabetes mellitus plasma levels of TNF α were greater than that of non-obese and type 2 diabetes mellitus free individuals and positively correlated with BMI and fasting blood glucose.⁵⁴ TNF α mRNA levels were shown to be higher in both SAT and VAT when compared to hepatic expression in severely obese subjects.⁵⁵ SAT, however, demonstrated higher levels of TNF α gene expression in metabolic syndrome with coronary artery disease (CAD) when compared to a control group without metabolic syndrome and CAD.⁵⁶

In obesity related type 2 diabetics treated with a TNF α -suppressor, levels of TNF α and other circulating proinflammatory adipokines decreased, but insulin profiles did not improve. This suggests additional adipokines may have been contributing to the observed insulin profiles or a larger dose of the suppressor was needed.⁵⁷ When patients with metabolic syndrome were given an TNF α -inhibitor over an extended period of time, fasting blood sugar improved, thus supporting a role of TNF α in obesity-related insulin resistance.⁵⁸ Moreover, endurance trained mice fed a high fat diet experienced a greater reduction in TNF α than resistance trained mice. Levels of TNF α were notably reduced in SCI individuals participating in a 12-week long arm crank exercise program,⁵⁹ as well as those undergoing functional electrical stimulation (FES) cycling for 10-weeks.⁶⁰

These results therefore suggest the secretion pattern of TNF α may be dependent on the degree of obesity and the adipokine exerts its effect by modulating metabolic homeostasis and inducing systemic inflammation. Moreover, exercise appears to positively influence TNF α activity in SCI. Nonetheless, few studies have examined the role of TNF α in neurogenic obesity in SCI, despite its pivotal role in metabolic dysfunction.

2. Interleukin-6

Interleukin-6 (IL-6) is secreted by a number of tissues including adipocytes and plays both a pro- and anti-

inflammatory role depending on the tissue and metabolic state.^{61–64} An estimated 10–35% of plasma IL-6 originates from adipocytes in humans, while other cells in adipose tissue, such as macrophages, produce the remaining portion.^{39,65} The gene expression and release of IL-6 directly related to the size of the adipocyte *in vivo* and *in vitro* studies, such that with an increase in obesity IL-6 is proportionally increased.⁶⁶ IL-6 production was strongly increased by TNF α activity in mice adipocytes *in vitro* such that it impaired action of insulin via the expression of SOCS3 ultimately inhibiting the PI3K-PKB cascade (Figure 1).^{64,67}

In both obese SCI and nondisabled individuals serum levels of IL-6 were significantly higher than that of non-obese healthy participants.^{18,68–70} Higher levels of IL-6 were reported in obesity-related insulin resistance with adipose tissue expressing elevated levels of IL-6 compared to a lean control group. In the same study, a strong correlation was noted between plasma IL-6 and both obesity and insulin resistance, whereas in SCI a positive correlation is noted between IL-6 and fasting insulin.^{19,71} A similar finding is noted in *in vivo* and *in vitro* where adipose-derived IL-6 positively correlates with insulin resistance.⁷² As with TNF α , elevated plasma levels of IL-6 associate with increased waist circumference, concentration of NEFA, and whole body mass.^{71,73} Interestingly, greater amounts of total body fat did not significantly correlate with IL-6 in SCI, most likely due to a small sample size.¹⁸

Lipid metabolism can also be modulated by IL-6. In obese individuals, IL-6 is chronically elevated in plasma and local adipose tissue concentrations and promotes adipocyte lipolysis through the activation of signal transducer and activator of transcription 3.^{74,75} During lipolysis, sphingosine kinase 1 (SPHK1) becomes upregulated in adipocytes leading to local inflammation and insulin resistance via the additional production of IL-6. When SPHK1 is repressed in mice it attenuates the release of IL-6 with subsequent reductions in adipose tissue inflammation.⁷⁶ Moreover, IL-6 is thought to alter the activity of lipoprotein lipase, an enzyme responsible for the uptake of circulating triglycerides in adipocytes. This consequently leads to elevated levels of circulating triglycerides and NEFA which both positively correlate with IL-6 (Figure 1).^{74,77}

In SCI, elevated levels of IL-6 are known to correlate with high-sensitivity c-reactive protein (hs-CRP), a hepatocyte-derived marker of systemic inflammation. hs-CRP is elevated in chronic SCI and is stimulated by both TNF α and IL-6 (Figure 1).^{19,41,42} Moreover, IL-6 is positively correlated with vascular cellular adhesion molecule-1 and intracellular adhesion molecule-1

which are indicators of vascular inflammation and are elevated in SCI compared to the nondisabled population.¹⁹ These cellular adhesion molecules attract circulating monocytes to the vascular wall which differentiate into proinflammatory cytokine secreting macrophages that further contribute to the vascular and systemic inflammation (Figure 1).⁶¹

When resveratrol, a drug used to reduce obesity-related inflammation, was added to subcutaneous adipocytes under inflammatory conditions, IL-6 levels decreased via inhibition of the NF- κ B pathway.⁷⁸ With a reduction in adipose tissue there is a decrease in IL-6 plasma levels⁷⁹ and a similar pattern is noted in SCI with exercise intervention.^{59,60,80} In addition to the proinflammatory role of IL-6, the signaling molecule has also been recognized anti-inflammatory agent.^{63,81} Exercise-induced release of IL-6 from skeletal muscle results in the secretion of anti-inflammatory cytokines from circulating monocytes. This increases skeletal muscle glucose uptake and fatty acid beta-oxidation during exercise through the stimulation of adenosine monophosphate-activated protein kinase (AMPK). Ultimately, leading to myogenesis and skeletal muscle hypertrophy.⁸² Collectively these results emphasize the importance of IL-6 in obesity and cardiometabolic dysfunction and stress the need of additional studies to elucidate the role of IL-6 in the pathophysiology of adipose tissue in SCI.

3. Plasminogen Activator Inhibitor-1

Plasminogen Activator Inhibitor-1 (PAI-1) is a primary inhibitor of fibrinolysis and proteolysis and belongs to the family of serine protease inhibitors. The protein specifically acts to inhibit tissue-type plasminogen activator and urokinase-type plasminogen activator leading to atherosclerosis, an increase in mean arterial pressure, and endothelial dysfunction (Figure 1).⁸³ Adipocytes,^{84,85} as well as cells of the stromal vascular fraction, such as macrophages,⁸⁶ vascular endothelial cells,^{83,87} and preadipocytes⁸⁸ synthesize and secrete PAI-1.

Plasma levels of PAI-1 are found elevated in obesity, insulin resistance, metabolic syndrome, and type 2 diabetes mellitus.^{86,89–91} In overweight subjects fed a fatty acid diet, glucose uptake was reduced and plasma PAI-1 concentrations increased resulting from a surge in macrophage-derived PAI-1 gene expression in adipose tissue.⁸⁶ In obese patients, VAT has a 5 times greater expression of PAI-1 than SAT, therefore further supporting the pathophysiological role of VAT in metabolic dysfunction.⁹¹ PAI-1 has been positively correlated with BMI, waist circumference, visceral fat area, and triglycerides, whereas the adipokine is

negatively correlated to HDL-C and the anti-inflammatory adipokine adiponectin in SCI.²¹ The association between PAI-1 and visceral adiposity has also been widely reported in the nondisabled population.⁹¹

With improvements in fitness, PAI-1 negatively correlates with HDL-C and glucose control, independent of weight loss.^{21,90} PAI-1 deficient mice given a high fat diet experience an increase in total energy expenditure, decrease weight gain, and improvements in insulin resistance.⁹² In humans, weight loss brings about decreases in plasma levels of PAI-1,^{90,93} however, such observations were not noted in SCI with exercise intervention.⁵⁹ As indicated by above, obesity derived elevated levels of PAI-1 may contribute to the development of obesity-related complications, but requires additional research in SCI.¹⁹

Animal versus human research in proinflammatory adipokines

The evidence outlined in this review demonstrates the variability of human and animal research in proinflammatory adipokines (Table 1). To the authors' knowledge, few animal studies have been validated in humans, thus making extrapolation and clinical application of the data difficult. In some cases animal models appear to predict or emulate human physiology. However, the observed responses in animal and human adipose tissue can occur through different inflammatory mechanisms and/or signaling pathways as a result of species dependent traits and varying genetic backgrounds. For example, the amount and distribution of the metabolically active brown adipose tissue considerably varies in rodents versus that of humans.⁹⁴ Obesity-related diseases in humans can greatly differ from the imposed disease model on laboratory animals where disease induction is typically performed in isolated environment while in humans manifestation is multifactorial.⁹⁵ Research involving animals, although subject to ethical considerations, allows for an array of physiological manipulations that are considered unethical in human subjects. While this research is necessary to advance our understanding of obesity-related inflammation and comorbidities, future studies need to investigate the validity of animal models as predictors of human pathognomies.

Evidence for proinflammatory adipokine research in spinal cord injury

To date, a limited number of proinflammatory adipokines have been examined in SCI-induced obesity. It is well documented that following SCI there is a substantial increase in adipose tissue which leads to a chronic,

systemic inflammatory state.^{18,21} This inflammatory state is thought to play a mechanistic role in the development of obesity-related comorbidities, such as type 2 diabetes mellitus and cardiovascular disease (Figure 1).¹⁸ Many adipose tissue-derived proinflammatory adipokines, including monocyte chemoattractant protein-1, resistin, and chemerin, have also been shown to interfere with homeostasis, directly correlate, and/or proportionally increase with accumulation of adipose tissue in nondisabled individuals (Figure 1 and Table 1). With a multitude of studies investigating the role of proinflammatory adipokines in the nondisabled population there is a growing need for research examining additional proinflammatory adipokines in the SCI population. This is especially critical given the unique physiology of SCI and alarming rates of neurogenic obesity.³

Conclusion

In summary, neurogenic obesity is the result of obligatory sarcopenia, anabolic deficiency, and sympathetic nervous system blunting that markedly reduces whole-body energy metabolism, resulting in adipose tissue accumulation.³ Profound metabolic dysfunction following SCI results from neurogenic obesity which causes chronic, systemic inflammation primarily through the overexpression of proinflammatory adipokines secreted as a result of the accumulation of adipose tissue. Elevated inflammatory adipokines serve as potential biomarkers for the development of obesity-related complications in populations with SCI and can be assessed by a simple blood test. Early identification and intervention may subsequently reduce the mortality risk associated with these diseases and ultimately prolong the lives of those living with a SCI.

The attenuation of adipose tissue through the use of dietary intervention and exercise may offer protective mechanisms against neurogenic obesity and its related comorbidities in the SCI population. In this regard, exercise may serve as an anti-inflammatory role in SCI. To date only three studies have examined the effects of exercise in reducing proinflammatory adipokines. However, these studies have only evaluated a limited number of adipokines without consideration of adiposity and demonstrate inconsistent results.^{59,60,80} In addition, even less research has been conducted investigating the effects of anti-inflammatory adipokines in obesity following SCI.^{59,80} More research, especially of the mechanistic nature, on proinflammatory adipokines is needed in SCI, as well as the effects of interventional weight loss on adipose tissue and its role in reducing its adipokines.

Disclaimer statements

Contributors Both authors contributed to the literature searches and writing of the review paper.

Funding None.

Declaration of Interest The authors report no declarations of interest.

Conflicts of interest None.

Ethics approval None.

Acknowledgments

The authors regret that all the research in this area could not be cited due to space limitations.

ORCID

Gary J Farkas <http://orcid.org/0000-0002-5482-6049>

References

- Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, *et al.* International standards for neurological classification of spinal cord injury (Revised 2011). *J Spinal Cord Med* 2011;34(6):535–46.
- Gorgey AS, Dolbow DR, Dolbow JD, Khalil RK, Castillo C, Gater DR. Effects of spinal cord injury on body composition and metabolic profile - part I. *J Spinal Cord Med* 2014;37(6):693–702.
- Gater DR. Obesity after spinal cord injury. *Phys Med Rehabil Clin N Am* 2007;18(2):333–351, vii.
- Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. *J Clin Invest* 1995;95(5):2111–9.
- Jo J, Gavrilova O, Pack S, Jou W, Mullen S, Sumner AE, *et al.* Hypertrophy and/or Hyperplasia: Dynamics of Adipose Tissue Growth. *PLoS Comput Biol* 2009;5(3). Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653640/>
- Gorgey A, Gater D. Prevalence of Obesity After Spinal Cord Injury. *Top Spinal Cord Inj Rehabil* 2007;12(4):1–7.
- Gorgey AS, Gater DR. Regional and relative adiposity patterns in relation to carbohydrate and lipid metabolism in men with spinal cord injury. *Appl Physiol Nutr Metab Physiol Appliquée Nutr Métabolisme* 2011;36(1):107–14.
- Rajan S, McNeely MJ, Warms C, Goldstein B. Clinical Assessment and Management of Obesity in Individuals With Spinal Cord Injury: A Review. *J Spinal Cord Med* 2008;31(4):361–72.
- Yarar-Fisher C, Chen Y, Jackson AB, Hunter GR. Body mass index underestimates adiposity in women with spinal cord injury. *Obes Silver Spring Md*. 2013;21(6):1223–5.
- Cirnigliaro CM, LaFountaine MF, Dengel DR, Bosch TA, Emmons RR, Kirshblum SC, *et al.* Visceral adiposity in persons with chronic spinal cord injury determined by dual energy X-ray absorptiometry. *Obes Silver Spring Md* 2015;23(9):1811–7.
- Gorgey AS, Mather KJ, Poarch HJ, Gater DR. Influence of motor complete spinal cord injury on visceral and subcutaneous adipose tissue measured by multi-axial magnetic resonance imaging. *J Spinal Cord Med* 2011;34(1):99–109.
- Sabour H, Javidan AN, Vafa MR, Shidfar F, Nazari M, Saberi H, *et al.* Obesity predictors in people with chronic spinal cord injury: an analysis by injury related variables. *J Res Med Sci Off J Isfahan Univ Med Sci* 2011;16(3):335–9.
- Spungen AM, Adkins RH, Stewart CA, Wang J, Pierson RN, Waters RL, *et al.* Factors influencing body composition in persons with spinal cord injury: a cross-sectional study. *J Appl Physiol Bethesda Md* 2003;95(6):2398–407.
- Sun X, Jones ZB, Chen X-M, Zhou L, So K-F, Ren Y. Multiple organ dysfunction and systemic inflammation after spinal cord injury: a complex relationship. *J Neuroinflammation* 2016;13(1):260.
- Anwar MA, Al Shehabi TS, Eid AH. Inflammogenesis of Secondary Spinal Cord Injury. *Front Cell Neurosci* 2016;10:98.
- David S, Zarruk JG, Ghasemlou N. Inflammatory pathways in spinal cord injury. *Int Rev Neurobiol* 2012;106:127–52.
- Hausmann ON. Post-traumatic inflammation following spinal cord injury. *Spinal Cord*. 2003;41(7):369–78.
- Manns PJ, McCubbin JA, Williams DP. Fitness, inflammation, and the metabolic syndrome in men with paraplegia. *Arch Phys Med Rehabil* 2005;86(6):1176–81.
- Wang T-D, Wang Y-H, Huang T-S, Su T-C, Pan S-L, Chen S-Y. Circulating levels of markers of inflammation and endothelial activation are increased in men with chronic spinal cord injury. *J Formos Med Assoc Taiwan Yi Zhi* 2007;106(11):919–28.
- Wang Y-H, Huang T-S, Liang H-W, Su T-C, Chen S-Y, Wang T-D. Fasting serum levels of adiponectin, ghrelin, and leptin in men with spinal cord injury. *Arch Phys Med Rehabil* 2005;86(10):1964–8.
- Maruyama Y, Mizuguchi M, Yaginuma T, Kusaka M, Yoshida H, Yokoyama K, *et al.* Serum leptin, abdominal obesity and the metabolic syndrome in individuals with chronic spinal cord injury. *Spinal Cord* 2008;46(7):494–9.
- Jung UJ, Choi M-S. Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease. *Int J Mol Sci* 2014;15(4):6184–223.
- BMI Classification [Internet]. World Health Organization. 2015 [cited 2015 Aug 6]. Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html
- Ogden CL, Lamb MM, Carroll MD, Flegal KM. Obesity and socioeconomic status in adults: United States, 2005–2008. *NCHS Data Brief* 2010;(50):1–8.
- Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 2014;311(8):806–14.
- Castro MJ, Apple DF, Hillegass EA, Dudley GA. Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first 6 months of injury. *Eur J Appl Physiol* 1999;80(4):373–8.
- Gorgey AS, Dudley GA. Skeletal muscle atrophy and increased intramuscular fat after incomplete spinal cord injury. *Spinal Cord* 2007;45(4):304–9.
- Shah PK, Stevens JE, Gregory CM, Pathare NC, Jayaraman A, Bickel SC, *et al.* Lower-extremity muscle cross-sectional area after incomplete spinal cord injury. *Arch Phys Med Rehabil* 2006;87(6):772–8.
- Dionysiotis Y, Stathopoulos K, Trovas G, Papaioannou N, Skarantavos G, Papagelopoulos P. Impact on bone and muscle area after spinal cord injury. *BoneKey Rep* 2015;4:633.
- Willems A, Paulson TAW, Keil M, Brooke-Wavell K, Goosey-Tolfrey VL. Dual-Energy X-Ray Absorptiometry, Skinfold Thickness, and Waist Circumference for Assessing Body Composition in Ambulant and Non-Ambulant Wheelchair Games Players. *Front Physiol* 2015;6:356.
- Han SH, Lee B-S, Choi HS, Kang M-S, Kim BR, Han Z-A, *et al.* Comparison of Fat Mass Percentage and Body Mass Index in Koreans With Spinal Cord Injury According to the Severity and Duration of Motor Paralysis. *Ann Rehabil Med* 2015;39(3):384–92.
- Mollinger LA, Spurr GB, el Ghatit AZ, Barboriak JJ, Rooney CB, Davidoff DD, *et al.* Daily energy expenditure and basal metabolic rates of patients with spinal cord injury. *Arch Phys Med Rehabil* 1985;66(7):420–6.
- Liu J, Fox CS, Hickson DA, May WD, Hairston KG, Carr JJ, *et al.* Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. *J Clin Endocrinol Metab* 2010;95(12):5419–26.
- Veilleux A, Caron-Jobin M, Noël S, Laberge PY, Tchernof A. Visceral Adipocyte Hypertrophy is Associated With Dyslipidemia Independent of Body Composition and Fat Distribution in Women. *Diabetes* 2011;60(5):1504–11.
- Pellegrinelli V, Rouault C, Rodriguez-Cuenca S, Albert V, Edom-Vovard F, Vidal-Puig A, *et al.* Human Adipocytes Induce

- Inflammation and Atrophy in Muscle Cells During Obesity. *Diabetes* 2015;64(9):3121–34.
- 36 Katsareli EA, Dedoussis GV. Biomarkers in the field of obesity and its related comorbidities. *Expert Opin Ther Targets* 2014;18(4):385–401.
 - 37 Curat CA, Wegner V, Sengenès C, Miranville A, Tonus C, Busse R, et al. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia* 2006;49(4):744–7.
 - 38 Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C, et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. *Biochem Biophys Res Commun* 2003;300(2):472–6.
 - 39 Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;112(12):1796–808.
 - 40 Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000;106(2):171–6.
 - 41 Lee MY, Myers J, Hayes A, Madan S, Froelicher VF, Perkash I, et al. C-reactive protein, metabolic syndrome, and insulin resistance in individuals with spinal cord injury. *J Spinal Cord Med* 2005;28(1):20–5.
 - 42 Gibson AE, Buchholz AC, Martin Ginis KA. C-Reactive protein in adults with chronic spinal cord injury: increased chronic inflammation in tetraplegia vs paraplegia. *Spinal Cord* 2008;46(9):616–21.
 - 43 Popa C, Netea MG, Riel PLCM van, Meer JWM van der, Stalenhoef AFH. The role of TNF- α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res* 2007;48(4):751–62.
 - 44 Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of Tumor Necrosis Factor- α and Increased Risk of Recurrent Coronary Events After Myocardial Infarction. *Circulation*. 2000;101(18):2149–53.
 - 45 Chen G, Goeddel DV. TNF-R1 signaling: a beautiful pathway. *Science*. 2002;296(5573):1634–5.
 - 46 Hoareau L, Bencharif K, Rondeau P, Murumalla R, Ravanian P, Tallet F, et al. Signaling pathways involved in LPS induced TNF α production in human adipocytes. *J Inflamm*. 2010;7(1):1.
 - 47 Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science* 1993;259(5091):87–91.
 - 48 Cawthorn WP, Sethi JK. TNF- α and adipocyte biology. *FEBS Lett* 2008;582(1):117–31.
 - 49 Xie L, Ortega MT, Mora S, Chapes SK. Interactive Changes between Macrophages and Adipocytes. *Clin Vaccine Immunol* 2010;17(4):651–9.
 - 50 Mooney RA, Senn J, Cameron S, Inamdar N, Boivin LM, Shang Y, et al. Suppressors of cytokine signaling-1 and -6 associate with and inhibit the insulin receptor. A potential mechanism for cytokine-mediated insulin resistance. *J Biol Chem* 2001;276(28):25889–93.
 - 51 de Alvaro C, Teruel T, Hernandez R, Lorenzo M. Tumor necrosis factor alpha produces insulin resistance in skeletal muscle by activation of inhibitor kappaB kinase in a p38 MAPK-dependent manner. *J Biol Chem* 2004;279(17):17070–8.
 - 52 Grant RW, Stephens JM. Fat in flames: influence of cytokines and pattern recognition receptors on adipocyte lipolysis. *Am J Physiol Endocrinol Metab* 2015;309(3):E205–213.
 - 53 Illán-Gómez F, González-Ortega M, Orea-Soler I, Alcaraz-Tafalla MS, Aragón-Alonso A, Pascual-Díaz M, et al. Obesity and Inflammation: Change in Adiponectin, C-Reactive Protein, Tumour Necrosis Factor-Alpha and Interleukin-6 After Bariatric Surgery. *Obes Surg* 2012;22(6):950–5.
 - 54 Mirza S, Hossain M, Mathews C, Martinez P, Pino P, Gay JL, et al. Type 2-diabetes is associated with elevated levels of TNF- α , IL-6 and adiponectin and low levels of leptin in a population of Mexican Americans: A cross-sectional study. *Cytokine* 2012;57(1):136–42.
 - 55 Moschen AR, Molnar C, Geiger S, Graziadei I, Ebenbichler CF, Weiss H, et al. Anti-inflammatory effects of excessive weight loss: potent suppression of adipose interleukin 6 and tumour necrosis factor α expression. *Gut* 2010;59(9):1259–64.
 - 56 Gormez S, Demirkan A, Atalar F, Caynak B, Erdim R, Sozer V, et al. Adipose Tissue Gene Expression of Adiponectin, Tumor Necrosis Factor- α and Leptin in Metabolic Syndrome Patients with Coronary Artery Disease. *Intern Med* 2011;50(8):805–10.
 - 57 Dominguez H, Storgaard H, Rask-Madsen C, Steffen Hermann T, Ihlemann N, Baunbjerg Nielsen D, et al. Metabolic and vascular effects of tumor necrosis factor- α blockade with etanercept in obese patients with type 2 diabetes. *J Vasc Res* 2005;42(6):517–25.
 - 58 Stanley TL, Zanni MV, Johnsen S, Rasheed S, Makimura H, Lee H, et al. TNF- α antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. *J Clin Endocrinol Metab* 2011;96(1):E146–150.
 - 59 Rosety-Rodriguez M, Camacho A, Rosety I, Fornieles G, Rosety MA, Diaz AJ, et al. Low-grade systemic inflammation and leptin levels were improved by arm cranking exercise in adults with chronic spinal cord injury. *Arch Phys Med Rehabil* 2014;95(2):297–302.
 - 60 Griffin L, Decker MJ, Hwang JY, Wang B, Kitchen K, Ding Z, et al. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. *J Electromyogr Kinesiol Off J Int Soc Electrophysiol Kinesiol* 2009;19(4):614–22.
 - 61 Andersson CX, Gustafson B, Hammarstedt A, Hedjazifar S, Smith U. Inflamed adipose tissue, insulin resistance and vascular injury. *Diabetes Metab Res Rev* 2008;24(8):595–603.
 - 62 Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF- α and IL-6. *Diabetes Res Clin Pract* 2005;69(1):29–35.
 - 63 Starkie R, Ostrowski SR, Jauffred S, Febbraio M, Pedersen BK. Exercise and IL-6 infusion inhibit endotoxin-induced TNF- α production in humans. *FASEB J Off Publ Fed Am Soc Exp Biol* 2003;17(8):884–6.
 - 64 Senn JJ, Klover PJ, Nowak IA, Zimmers TA, Koniaris LG, Furlanetto RW, et al. Suppressor of cytokine signaling-3 (SOCS-3), a potential mediator of interleukin-6-dependent insulin resistance in hepatocytes. *J Biol Chem* 2003;278(16):13740–6.
 - 65 Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor- α , in vivo. *J Clin Endocrinol Metab* 1997;82(12):4196–200.
 - 66 Sopasakis VR, Sandqvist M, Gustafson B, Hammarstedt A, Schmelz M, Yang X, et al. High local concentrations and effects on differentiation implicate interleukin-6 as a paracrine regulator. *Obes Res* 2004;12(3):454–60.
 - 67 Rotter V, Nagaev I, Smith U. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor- α , overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem* 2003;278(46):45777–84.
 - 68 Roytblat L, Rachinsky M, Fisher A, Greemberg L, Shapira Y, Douvdevani A, et al. Raised Interleukin-6 Levels in Obese Patients. *Obes Res* 2000;8(9):673–5.
 - 69 Hansen D, Dendale P, Beelen M, Jonkers RAM, Mullens A, Corluy L, et al. Plasma adipokine and inflammatory marker concentrations are altered in obese, as opposed to non-obese, type 2 diabetes patients. *Eur J Appl Physiol* 2010;109(3):397–404.
 - 70 Krause JS, DiPiro ND, Saunders LL, Newman SD, Banik NL, Park S. Allostatic Load and Spinal Cord Injury: Review of Existing Research and Preliminary Data. *Top Spinal Cord Inj Rehabil* 2014;20(2):137–46.
 - 71 Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol Endocrinol Metab* 2001;280(5):E745–751.
 - 72 Bastard J-P, Maachi M, Van Nhieu JT, Jardel C, Bruckert E, Grimaldi A, et al. Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. *J Clin Endocrinol Metab* 2002;87(5):2084–9.
 - 73 Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. *Obes Res* 2001;9(7):414–7.

- 74 van Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P, *et al.* Interleukin-6 stimulates lipolysis and fat oxidation in humans. *J Clin Endocrinol Metab* 2003;88(7):3005–10.
- 75 Trujillo ME, Sullivan S, Harten I, Schneider SH, Greenberg AS, Fried SK. Interleukin-6 Regulates Human Adipose Tissue Lipid Metabolism and Leptin Production in Vitro. *J Clin Endocrinol Metab* 2004;89(11):5577–82.
- 76 Zhang W, Mottillo EP, Zhao J, Gartung A, VanHecke GC, Lee J-F, *et al.* Adipocyte Lipolysis Stimulated Interleukin-6 Production Requires Sphingosine kinase 1 activity. *J Biol Chem* 2014; jbc.M114.601096.
- 77 Karpe F, Dickmann JR, Frayn KN. Fatty Acids, Obesity, and Insulin Resistance: Time for a Reevaluation. *Diabetes* 2011;60(10):2441–9.
- 78 Zagotta I, Dimova EY, Debatin K-M, Wabitsch M, Kietzmann T, Fischer-Posovszky P. Obesity and inflammation: reduced cytokine expression due to resveratrol in a human in vitro model of inflamed adipose tissue. *Inflamm Pharmacol* 2015;79.
- 79 Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, *et al.* Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *J Clin Endocrinol Metab* 2000;85(9):3338–42.
- 80 Bakkum AJT, Paulson TAW, Bishop NC, Goosey-Tolfrey VL, Stolwijk-Swüste JM, van Kuppevelt DJ, *et al.* Effects of hybrid cycle and handcycle exercise on cardiovascular disease risk factors in people with spinal cord injury: A randomized controlled trial. *J Rehabil Med* 2015;47(6):523–30.
- 81 Carey AL, Steinberg GR, Macaulay SL, Thomas WG, Holmes AG, Ramm G, *et al.* Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. *Diabetes* 2006; 55(10):2688–97.
- 82 O'Neill HM. AMPK and Exercise: Glucose Uptake and Insulin Sensitivity. *Diabetes Metab J* 2013;37(1):1–21.
- 83 Singh P, Peterson TE, Barber KR, Kuniyoshi FS, Jensen A, Hoffmann M, *et al.* Leptin upregulates the expression of plasminogen activator inhibitor-1 in human vascular endothelial cells. *Biochem Biophys Res Commun* 2010;392(1):47–52.
- 84 Tamura Y, Kawao N, Yano M, Okada K, Okumoto K, Chiba Y, *et al.* Role of plasminogen activator inhibitor-1 in glucocorticoid-induced diabetes and osteopenia in mice. *Diabetes* 2015;64(6):2194–206.
- 85 Cox CL, Stanhope KL, Schwarz JM, Graham JL, Hatcher B, Griffen SC, *et al.* Circulating Concentrations of Monocyte Chemoattractant Protein-1, Plasminogen Activator Inhibitor-1, and Soluble Leukocyte Adhesion Molecule-1 in Overweight/ Obese Men and Women Consuming Fructose- or Glucose-Sweetened Beverages for 10 Weeks. *J Clin Endocrinol Metab* 2011;96(12):E2034–8.
- 86 Kishore P, Li W, Tonelli J, Lee D-E, Koppaka S, Zhang K, *et al.* Adipocyte-Derived Factors Potentiate Nutrient-Induced Production of Plasminogen Activator Inhibitor-1 by Macrophages. *Sci Transl Med* 2010;2(20):20ra15–20ra15.
- 87 Smyth JV, Rooney OB, Dodd PD, Walker MG. Production of plasminogen activator inhibitor-1 by human saphenous vein endothelial cells seeded onto endarterectomy surfaces in vitro. *J Vasc Surg* 1997;25(4):722–5.
- 88 Crandall DL, Quinet EM, Morgan GA, Busler DE, McHendry-Rinde B, Kral JG. Synthesis and secretion of plasminogen activator inhibitor-1 by human preadipocytes. *J Clin Endocrinol Metab* 1999;84(9):3222–7.
- 89 Ekström M, Liska J, Eriksson P, Sverremark-Ekström E, Tornvall P. Stimulated in vivo synthesis of plasminogen activator inhibitor-1 in human adipose tissue. *Thromb Haemost* 2012;108(3):485–92.
- 90 Belalcazar LM, Ballantyne CM, Lang W, Haffner SM, Rushing J, Schwenke DC, *et al.* Metabolic Factors, Adipose Tissue, and Plasminogen Activator Inhibitor-1 Levels in Type 2 Diabetes Findings From the Look AHEAD Study. *Arterioscler Thromb Vasc Biol* 2011;31(7):1689–95.
- 91 Alessi M-C, Juhan-Vague I. PAI-1 and the metabolic syndrome: links, causes, and consequences. *Arterioscler Thromb Vasc Biol* 2006;26(10):2200–7.
- 92 Ma L-J, Mao S-L, Taylor KL, Kanjanabuch T, Guan Y, Zhang Y, *et al.* Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. *Diabetes* 2004;53(2):336–46.
- 93 Primrose JN, Davies JA, Prentice CR, Hughes R, Johnston D. Reduction in factor VII, fibrinogen and plasminogen activator inhibitor-1 activity after surgical treatment of morbid obesity. *Thromb Haemost* 1992;68(4):396–9.
- 94 Gesta S, Tseng Y-H, Kahn CR. Developmental Origin of Fat: Tracking Obesity to Its Source. *Cell* 2007;131(2):242–56.
- 95 Grundy SM. Multifactorial causation of obesity: implications for prevention. *Am J Clin Nutr* 1998;67(3 Suppl):563S–72S.
- 96 Balistreri CR, Caruso C, Candore G, Balistreri CR, Caruso C, Candore G. The Role of Adipose Tissue and Adipokines in Obesity-Related Inflammatory Diseases, The Role of Adipose Tissue and Adipokines in Obesity-Related Inflammatory Diseases. *Mediat Inflamm Mediat Inflamm* 2010:e802078.
- 97 Nakamura K, Fuster JJ, Walsh K. Adipokines: a link between obesity and cardiovascular disease. *J Cardiol* 2014;63(4):250–9.
- 98 Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011;11(2):85–97.
- 99 Chakaroun R, Raschpichler M, Klötting N, Oberbach A, Flehmig G, Kern M, *et al.* Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. *Metabolism* 2012;61(5):706–14.
- 100 Khoo J, Dhamodaran S, Chen D-D, Yap S-Y, Chen RY, Tian H-H. Exercise-Induced Weight Loss is More Effective than Dieting for Improving Adipokine Profile, Insulin Resistance, and Inflammation in Obese Men. *Int J Sport Nutr Exerc Metab* 2015;25(6):566–75.
- 101 Sun G, Bishop J, Khalili S, Vasdev S, Gill V, Pace D, *et al.* Serum visfatin concentrations are positively correlated with serum triacylglycerols and down-regulated by overfeeding in healthy young men. *Am J Clin Nutr* 2007;85(2):399–404.