EDITORIAL

Adiposity and spinal cord injury

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Abstract

The drastic changes in body composition following spinal cord injury (SCI) have been shown to play a significant role in cardiovascular and metabolic health. The pattern of storage and distribution of different types of adipose tissue may impact metabolic health variables similar to carbohydrate, lipid and bone metabolism. The use of magnetic resonance imaging provides insights on the interplay among different regional adipose tissue compartments and their role in developing chronic diseases. Regional adipose tissue can be either distributed centrally or peripherally into subcutaneous and ectopic sites. The primary ectopic adipose tissue sites are visceral, intramuscular and bone marrow. Dysfunction in the central nervous system following SCI impacts the pattern of distribution of adiposity especially between tetraplegia and paraplegia. The current editorial is focused primarily on introducing different types of adipose tissue and establishing scientific basis to develop appropriate dietary, rehabilitation or pharmaceutical interventions to manage the negative consequences of increasing adiposity after SCI. We have also summarized the clinical implications and future recommendations relevant to study adiposity after SCI.

Key words: Adiposity; Magnetic resonance imaging; Dual-energy X-ray absorptiometry; Ectopic adiposity; Visceral and subcutaneous adiposity; Intramuscular fat; Spinal cord injury

Core tip: The focus of this current editorial is to introduce different adipose tissue types that may impose

significant health risks to individuals with spinal cord injury (SCI). Accurate measuring of this depot of ectopic adipose tissue may require special knowledge; however, it is important considering the dramatic changes in body composition and the extensive loss in skeletal muscle tissue below the level of injury. The clinical implications of studying adipose tissue may encourage further research to decipher the mechanistic links with the metabolic profile after SCI. Our current knowledge is limited and rehabilitation strategies are still pre-mature in targeting ectopic adiposity after SCI.

INTRODUCTION

Adipose tissue is one of the main types of connective tissue in the body and is the storage site of triglycerides. It is not only served as an energy reservoir, but it has been recently considered as the largest endocrine gland in the body[1,2]. The endocrine properties are related to the secretion of regulatory proteins similar to leptin, cytokines and adiponectin that are likely to influence whole body metabolism, energy intake as well as insulin sensitivity[2]. Inflammatory biomarker factors similar to interlukin 6, tumor necrosis factor alpha and C-reactive proteins which are likely to interact with various systems can trigger insulin resistance[2,3]. The inflammatory nature of adipose tissue has been linked to other comorbidities similar to type 2 diabetes mellitus, cancer and cardiovascular disease. Additionally, adipose tissues secrete number of active peptides called adipokines[3].

Interest in studying adipose tissue physiology and anatomical distribution has stemmed from its closest association with disturbance in metabolic profile including carbohydrate, lipid, and bone metabolism[3-7]. Most recently the link between adipose tissue and bone health has been recognized after spinal cord injury (SCI)[7]. This link may contribute to our understanding of different pathways that lead to the development of obesity and osteoporosis. Moreover, the role of exercise in adipose tissue utilization as a primary source of fuel is an active area of continuous research investigation[8-11]. Excessive adipose tissue accumulation imposes significant health risks to populations with physical disability leading to poor quality of life and short life-span. Imbalance between energy intake and energy expenditure may lead to excessive adipose tissue accumulation, a phenomenon which is referred to as obesity[12]. Obesity is further complicated by other factors similar to physical activity, genetic, socio-economical and educational factors. According to a survey conducted by the Center for Disease Control,

more than one-third (34.9%) of adults in the United States are considered obese[13].

SCI is a medical condition resulting from direct or indirect aggravation or insult to the neural pathway located in the vertebral column. The disruption in the efferent and afferent neural transmission between the cortex and the periphery leads to the paralysis of skeletal and smooth muscles as well as somatosensory loss of pain, touch and temperature sensation below the level of injury. A person with SCI is considered to be on the lowest end of the spectrum of physical activity as determined by the lowest oxygen uptake during peak exercise activity[14]. The low level of physical activity, significant muscle loss with changes in regional and total body composition, dysfunction in the autonomic nervous system and diminished anabolic hormones are a typical phenotype profile for a person with SCI[4,15,16].

The significant loss in lean mass within the first year of injury is accompanied with continuous increase in adipose tissue accumulation representing significant health risks after SCI[17]. Time since injury is strongly associated with a greater loss of lean tissue after SCI[17]. A strong effect of time since injury was identified in the legs and total body of monozygotic twins with paraplegia compared to their non-disabled (ND) co-twins, thereby eliminating age and genetic factors, essentially isolates the effect of SCI[18].

The purpose of this editorial is to introduce different types of adipose tissue distribution and their link to health consequences after SCI[19-22]. Considering the role of adipose tissue in the metabolic health variables after SCI, we sought to summarize the available evidence on different forms of adipose tissue. We highlighted the basic findings relevant to ectopic adipose tissue [visceral fat (VAT), intramuscular fat (IMF) and bone marrow fat (BMF)] in persons with SCI and the technical procedures regarding the use of magnetic resonance imaging (MRI) in measuring ectopic adipose tissue[19,22]. The difference in terminology between intermuscular (IeMF) and IMF was addressed as well as the significance of measuring visceral and bone marrow adiposity (Figures 1 and 2).

Finally, the clinical implications and future directions of measuring different types of adipose tissue and cardio-metabolic health were acknowledged. We have also realized the significance of exercise and dietary interventions in addressing the complications of reduction in level of physical activity after SCI. Encouragement to expand leisure time physical activity may help to counteract reduced level of energy expenditure and balanced their daily caloric intake.

For this editorial, we would like to distinguish between the terms "obesity" and "adiposity" relevant to the SCI population. Obesity is simply a metabolic disorder resulted from an imbalance between energy intake and expenditure. Obesity is simply defined using body mass index (BMI), waist and abdominal circumferences. These anthropometric criteria have
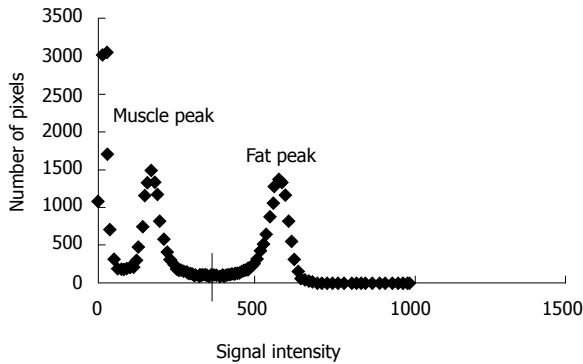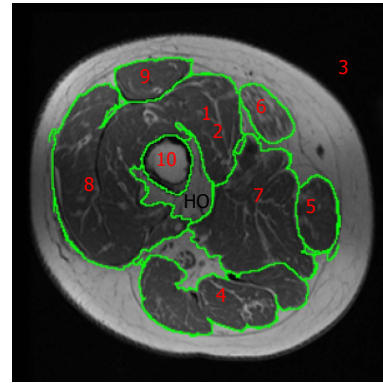
Figure 1 Histogram analysis of the whole thigh region representing both muscle (left) and fat (right) peaks as well as the mid-point signal intensity that is used a cut-off point to separate between muscle or inter-intra-muscular fat pixels.

Figure 2 A representative transaxial magnetic resonance imaging of the mid-thigh of a T4 individual with complete spinal cord injury representing different region of interests. Note the white adipose tissue infiltrated between individual muscle groups IMF as well as the white adipose tissue infiltrated within individual muscle IMF. We have collectively referred to both of them as IMF. Also note the HO extended from the bone marrow. [1]Three vasti muscles (m); [2]Vastus intermedius (m); [3]Image background; [4]Hamstrings (m); [5]Gracilis (m); [6]Sartorius (m); [7]Adductors (m); [8]Vastus lateralis (m); [9]Rectus femoris (m); [10]Cortical bone and bone marrow. IMF: Interamuscular fat; HO: Heterotrophic ossification.

not been well validated in the field of body composition and SCI, with a considerable debate about its efficacy in identifying those at risks of developing cardio-metabolic complications. It is well established that BMI underestimates the percentage fat mass (FM) in persons with SCI, with a continuous effort to develop a population specific BMI criteria[17]. The term adiposity refers to infiltration or storage of adipose tissue in subcutaneous or ectopic sites due to inactivity, disruption in hormonal secretion, altered body composition and poor nutritional choices after SCI. Studying whole and regional adiposity may need specialized body composition assessment techniques to accurately quantify adiposity after SCI. Although the prevalence of obesity may easily exceed two-thirds of the SCI population[23]; we believe that that the SCI population suffers from excessive adiposity that exceeds 30% of the whole body mass[6,17]. This may be true in 50% of the SCI population despite having normal BMI, which leads to significant metabolic and health implications[6].

TYPES OF ADIPOSE TISSUE

Advances in imaging technology similar to the use of MRI, ultrasound and dual-energy X-ray absorptiometry (DXA) facilitate the study of the distribution of regional adiposity[19-22]. DXA scans are commonly used in the clinical settings to measure total, regional body composition and bone mineral density or content. However, DXA is limited in distinguishing between subcutaneous adipose tissue (SAT) and ectopic adipose tissue[6]. The anatomy and distribution of adipose tissue is of particular interest to the metabolic health after SCI[5-7,16]. Triglycerides can be either stored in subcutaneous or ectopic sites similar to the peritoneum, visceral adipose tissue (VAT), in the liver (steatosis), in the muscle such as IMF or IeMF and in the bone marrow as BMF. The mechanisms by which triglycerides are stored in subcutaneous or ectopic sites are poorly understood; however, it is linked to genetic and lifestyle factors. Adopting an active lifestyle including routine exercise

is likely to reduce ectopic adipose tissue storage in the general population as well as in persons with SCI[9,10]. This is also accompanied with mitigating the negative consequences of ectopic adipose tissues on the metabolic profile. The role of exercise on SAT is still questionable[9].

Compared with non-disabled (ND) individuals, Spungen *et al*[17] showed that the individuals with SCI were 13% fatter per unit of BMI (kg/m^2). Moreover, the total body fat was 10% greater in the group with tetraplegia and 12% greater in the group with paraplegia compared to ND individuals. Also, percent FM in the arms of tetraplegics was 8% greater than individuals with paraplegia[17]. Persons with SCI are likely to have more than 30% FM of the total body mass; that are stored at the central or peripheral site[23]. The central distribution of adipose tissue may represent up to 25% of total body FM[22]. Gorgey and Gater[6] have highlighted the significance of studying regional and relative adiposity and their associations to metabolic health variables after SCI.

Central adipose tissue

The central adipose tissue refers to quantifying trunk FM which can further be sub-divided into SAT and VAT. In analyzing VAT and SAT volumes, our laboratory has taken advantage of analyzing multiple axial slices acquired during MRI. We have previously shown that using a single axial slice may inaccurately reflect the true volumetric distribution of VAT and SAT[22]. After measuring the CSA of series of axial images, the volume of VAT or SAT can be calculated by summing up all the measured areas. The volume (cm^3) is calculated using the following equation = $(A_1d_{1-2} + A_2d_{2-3} + A_3d_{3-4}........A_nd_{n-n+1})$ after considering the thickness of the slice. The "A" letter refers to the CSA of a single axial image and "d" refers to the distance (cm) of inter-space
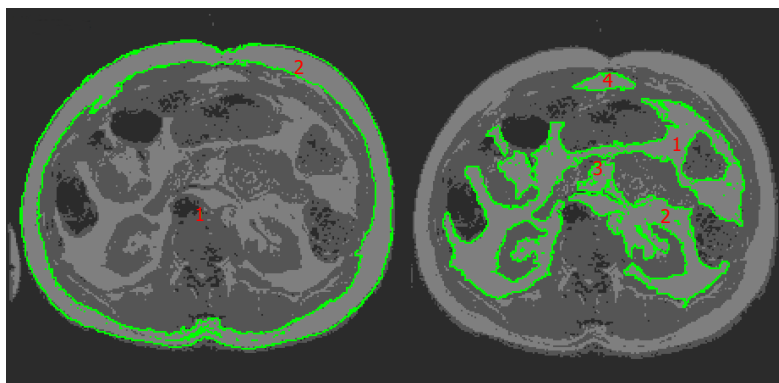
Figure 3 A representative magnetic resonance imaging analysis of subcutaneous and visceral adipose tissues in a person with spinal cord injury. Note the tracing of visceral adipose tissue within the region of interest. The numbers 1, 2, 3 and 4 refer to the visceral fat (VAT) cross-sectional areas of disconnected regions. These 4 regions are later summed to have the total VAT area in the entire region. VAT: Visceral adipose tissue.

between two corresponding axial images.

SAT: SAT is layered superficial to the outer muscular wall of the abdominal region and skeletal muscle, and immediately below the dermal layer of the skin[5,22]. Abdominal SAT is superficial to the abdominal and back muscles and lies beneath the hypodermis. SAT is measured by tracing the outer edge of the abdominal region (hypodermis) and along the outermost point of the muscular abdominal wall. The area in between these two traces will be considered the cross-sectional area (CSA) in cm^2 of this slice (Figure 3).

The level of injury strongly determines the severity of SCI as well as the associated changes in body composition. Individuals with tetraplegia population have a greater leg FM/trunk FM (45%) and leg FM/body FM (26%) and lower trunk FM/body FM (29%) ratios than individual with paraplegia[6]. This may suggest that persons with tetraplegia have the tendency to accumulate greater leg FM compared to those with paraplegia. Surprisingly, persons with tetraplegia have a lower ratio of trunk FM to whole body FM compared to persons with SCI[6]. These findings were confirmed when MRI was used to separate trunk VAT from SAT. The SAT CSA was non-significantly greater in persons with paraplegia compared to tetraplegia[24]. The hyperactivity of sympatho-adrenergic peripheral innervation to SAT may be responsible for the lower trunk adipose tissue in persons with tetraplegia and may explain the tight association that was documented between SAT CSA and lipid profile[24,25].

VAT: VAT is defined as intra-abdominal fat bound by parietal peritoneum or transversalis fascia, excluding the vertebral column and paraspinal muscles[5,22]. VAT may extend from the xyphoid process of the sternum to both greater trochanters of the femoral bones. VAT is measured by tracing out the innermost muscles of the abdominal cavity and the other abdominal organs present in a single slice. The area is quantified in cm^2 which shows the amount of VAT present within the abdominal organs.

It is important to be meticulous and not trace over any fat tissue as it will yield inaccurate results. Increase in VAT accumulation has been identified as an independent risk factor of developing cardiovascular disease, insulin resistance and mortality[26]. This is mainly because of the close proximity of the VAT to the portal circulation. Further analysis using MRI showed that about 6% of whole body FM is VAT and 10% is SAT[22]. Persons with SCI have 58% and 48% greater VAT CSA and VAT/SAT CSA compared to ND controls[27]. It is apparent that VAT and increase VAT/SAT ratio are likely to have detrimental effects on the metabolic profile after SCI[5].

The pattern of VAT distribution may vary greatly among individuals with SCI. It is likely to be impacted by the level of injury and the de-innervation of the anterior abdominal muscles[24]. Further analysis based on the level of the injury did not reveal major differences in VAT between persons with paraplegia and tetraplegia[24]. However, the sample size was limited and future studies need to consider large sample size to study the differences in central adiposity based on the level of injury.

There are several points that need to be considered when using MRI to measure central adiposity in persons with SCI including the type of the injury, date of the injury, spinal fusion, and ability of the persons to hold his or her breath. All of these factors may influence the quality of the scan and may interfere with the ability of the examiner to accurately analyze the images[5,22,24]. For example, a gunshot wound may lead to bullet fragments in the spinal canal that will be of high risk to be exposed to a magnetic field. This bullet fragments may accidently move and lead to further damage to the intact cord or the surrounding blood supplies. A person with high level of injury, similar to C5, may lack the ability to hold his breath for 20-22 s to capture the whole trunk region. This may require the examiner to break the whole scan into multiple scans to allow short breath holding time that does not exceed 10 s. Other limitations may include the exact positioning of the

participant inside the magnet mainly because of pelvic or trunk obliquity or uncontrolled spasticity that may be triggered before or during the scans and require special handling from positioning and stabilizing lower extremities, this is specifically important to accurately match the pre and post-MRI images in a longitudinal study.

The scans are captured from the xyphoid process to both greater trochanters. It becomes apparent that using a flexible trunk coil compared to the whole body magnet improves the quality and resolution of the captured images as well as higher signal to noise ratio. It is highly recommended that multiple axial images are sequenced to ensure the appropriate anatomical organization before the analysis. This is a crucial step before measuring the volume of the SAT or VAT. Different software programs may be available allowing appropriate segmentation of VAT and SAT in a single axial slice to measure the CSA without including other visceral regions similar to the intestines or the blood vessels in the region of interest.

Studying SAT and VAT distribution have revealed two body composition phenotypes[5,6]. The first phenotype is likely to store adipose tissue in subcutaneous compared to visceral sites and this phenotype may protect against developing metabolic disorders. The second phenotype has a greater tendency to store adipose tissue in visceral sites with the tendency to develop insulin resistance, dyslipidemia and other metabolic disorders. The exact mechanisms behind these two phenotypes have yet to be deciphered. Anecdotal evidence from our laboratory suggests that gender may play a definite role in the distribution of VAT and SAT after SCI. Women with SCI have greater SAT and smaller VAT CSAs than men with SCI (Gorgey *et al* unpublished results). This may shed the light on the significance of studying hormonal differences and adiposity after SCI.

Peripheral adipose tissue

The peripheral distribution may vary between arms and legs. Legs are likely to have on average 34%-38% of the whole body FM[6,17]. The increase storage of adipose tissue is primarily accompanied with process of lower-extremity disuse, skeletal muscle atrophy and autonomic nervous system dysfunction[16]. This will eventually contribute to infiltration and accumulation of adipose tissue in non-subcutaneous sites (muscle and bone). This ectopic accumulation of adipose tissue leads to serious metabolic consequences after SCI. The use of MRI manages to segment and compartmentalize adipose tissue based on its high signal intensity from the atrophic skeletal muscles, allowing accurate quantification of muscle size in response to disuse and exercise[9,10,16]. In our laboratory (Figures 1 and 2), we have managed to distinguish between IMF, IeMF, subfacial and SAT accumulation in persons with SCI[9,10].

The storage of triglycerides in ectopic locations is linked with chronic inflammation, impaired glucose tolerance, increased total cholesterol, and decreased strength and mobility[1,2]. There is growing interest in studying different peripheral adipose tissue compartments to determine its link to metabolic profile after SCI[6,26]. Moreover, there is anecdotal evidence supporting the notion that nutritional status and dietary habits may influence these compartments; because persons with SCI are likely to consume high fat diet, which is close to 40% of the total caloric intake[9,28].

IMF *vs* IeMF: Previous studies have focused on the metabolic impact of intramyocellular lipid (IMCL) content (*i.e.*, lipid droplets stored in the cytoplasm of muscle cells) and extramyocellular lipid (EMCL) content, which can reliably be assessed by proton magnetic resonance spectroscopy (1 H-MRS). The deposition of IMCL could be altered in prediabetic or obese subjects, and could probably be associated with insulin resistance[29,30]. A study that compared persons with paraplegia to ND controls showed that IMCL was not different in the paralyzed muscles. However, the study noted greater EMCL in the paraplegic muscles, which was negatively associated with insulin sensitivity. The same study noted a 57% lower succinate dehydrogenase activity in person with SCI compared to controls[29].

The definition of IMF refers to infiltration of adipose tissue within individual muscle. It is measured by determining the attenuation property of computerized tomography (CT) or the signal intensity of MRI[31,32]. The storage of IMF is dramatically elevated after SCI and it is closely linked to other fat compartments, especially to VAT (Figures 2 and 3). It seems that IMF and VAT share an analogous pattern in distribution and association with insulin sensitivity[5,26,27,31,32]. Using MRI, Gorgey and Dudley[16] showed that IMF was 126% greater in persons with incomplete SCI compared to the matched ND controls. IMF CSA continued to increase in the 3-mo follow-up MRI scan[16]. Elder *et al*[31] reported that IMF and skeletal muscle atrophy in the thigh accounted for 70% of glucose intolerance after SCI. The same study noted that IMF and subfacial fat appeared to be increased in chronic individuals with SCI when compared to ND controls[31]. It is interesting to note that unlike SAT, IMF decreases in response to spasticity and exercise activity similar to resistance training[9,33].

Although IMF is likely to be visualized, it is nearly impossible to be traced in order to be quantified. IeMF refers to fatty infiltration of adipose tissue between individual muscle groups[30]. This fatty infiltration is highly accumulated in the posterior compartment of the thigh and visually can be traced or separated based on its high signal intensity (Figure 2). A controversial area of debate is whether MRI can be used to quantify IMF. The histographic analysis has helped differentiating between IeMF and IMF infiltration (Figure 1).

Reliance on histographic analysis can help distinguish between muscle from fat voxels (*i.e.*, the volume of a pixel). This histographic analysis allows previous

quantification of IMF in individuals' thigh muscles. We have previously felt more comfortable referring to adipose tissue as IMF and not IeMF because it composed both the fat infiltrated within the muscle as well as the fat infiltrated between individual muscles. This may further shed the light on the significance of separating IMF from IeMF accumulation and the associated links with metabolic consequences after SCI.

The histogram (pixel number versus signal intensity) produced from analysis of the whole thigh (muscle, fat and bone) showed two distinct muscle and fat peaks based on the variations in the signal intensity to the magnetic field[9,10,16,33]. The ranges and values for these peaks differ from individual to individual. The left peak was distinct, thin, and representing skeletal muscle area. This is due to the lower signal intensity that skeletal muscle is represented through MRI. The higher signal intensity peak is on the right side and representing the fat peak (Figure 1).

There is a greater infiltration of IMF most notably in the areas of the quadriceps, hamstrings, and adductor muscles. After determining the cut-off point between muscle and fat based on the signal intensity, the percentage of IMF within each individual muscle can be accurately measured. A crucial point that needs to be considered is measuring muscle size after accounting for IMF percentage. Failure to separate IMF from the measured muscle CSA overestimates the actual skeletal muscle size. For example, measuring the muscle CSA of the three vasti equated to 29.34 cm^2. After applying the muscle-fat cut off technique, the percentage IMF was 26.25% with an area of 7.702 cm^2. This means that failure to account for IMF overestimated muscle size by more than 26%. The accumulation of IMF within muscle has been previously considered in measuring muscle size in individuals with SCI[9,10,16,33].

From the rehabilitation point of view, IMF may impede the progression of the current in the exercising muscles during neuromuscular electrical stimulation[34]. This may result in an unnecessary increase of the amplitude of the current of neuromuscular electrical stimulation and lead to rapid muscle fatigue of the paralyzed muscles.

Bone marrow adipose tissue: The relationship between the alarming prevalence of obesity and osteoporosis is considered an area of a growing research interest. It is unclear whether there is a common origin from where excessive adiposity and continuous loss in bone mass originates after SCI. The mesenchymal progenitor stem cells (MSC) can be differentiated based on the mechanical stimulus applied into either bone and muscle cells or adipose tissue[35-37]. This differentiation may be very important in providing the appropriate mechanical stimulus necessary for the development of muscle and bone tissue compared to adipose tissues after SCI. Our initial observation showed that persons with motor complete SCI had 2-3 times bone marrow adipose tissue compared to matched able-bodied controls; primarily because of unloading on lower extremities[7]. This is accompanied with 1.5-2 times lower cortical bone CSA in persons with SCI compared to able-bodied controls[7]. Moreover, the bone marrow adipose tissue was inversely related to the bone mineral density and bone mineral content as measured by DXA. This preliminary evidence suggests that there is inverse relationship between increasing bone marrow adiposity and both cortical bone as well as bone mineral density[7]. This may suggest that MSC need to be considered as a therapeutic anatomical target for future interventions to cease the progress in adiposity and osteoporosis after SCI.

Anecdotal evidence based on recent imaging analysis showed that MSC differentiation into bone marrow adiposity can leak outside and contribute to the development of intermuscular adipose tissue or IMF infiltration in the atrophic skeletal muscle. In Figure 3, we have traced an abnormal growth of heterotrophic ossification (HO) within the thigh region. It is clear that this HO has been developed as a leakage from the bone marrow region. This abnormal bone growth within the skeletal muscle has a signal intensity that it is closely related to the signal intensity of the yellow bone marrow and lower than that of adipose tissue. This may speculatively suggest that HO development started as an abnormal fatty infiltration from that yellow marrow followed by calcium deposition in this region.

White vs brown adipose tissue
It has been discovered that humans contain both white and brown adipose tissue which possess two distinct developmental origins and functions[38-42]. The brown adipose tissue has yet to be studied in humans with SCI; however, its potential contribution to increase the metabolic rate is important considering the prevalence of obesity after SCI.

White adipose tissue: White adipose tissue takes on a critical role in maintaining energy homeostasis throughout the entire body. Homeostasis is maintained by storing triglycerides when energy is in surplus, releasing fatty acids as fuel during energy storage, and secreting adipokines which regulate glucose and lipid metabolism[2,38]. Recent studies indicate that white adipose tissue serves as an active endocrine organ which secretes numerous hormones, cytokines, and chemokines that are essential for regulating energy homeostasis in the body[2]. Two specific hormones released by white adipose tissue are leptin and adiponectin. Leptin is positively associated with white adipose tissue and serves to suppress food intake and increase energy expenditure[2]. The hormone adiponectin is inversely correlated with white adipose tissue and has been considered a promising biomarker for the indication of insulin sensitivity[2,39]. In addition to these secreting hormones, white adipose tissue can

also secrete proinflammatory factors including tumor necrosis factor alpha, interleukin-6, and monocyte chemotactic protein-1[2]. The various adipose tissue compartments, such as subcutaneous and visceral depots follow a distinct pattern of hormone and adipokine secretion[39]. The adipocytes in subcutaneous depots have a higher capacity for adipogenesis and differentiate more rapidly compared to visceral depots. White adipose tissue in the visceral abdominal region has been shown to increase insulin resistance, thereby, it is less harmful to store white adipose tissue in subcutaneous compartment compared to the visceral region[38].

Brown adipose tissue: Brown adipose tissue contains lipid droplets and is rich in mitochondria[40-42]. The thermogenetic adipocytes increase energy expenditure through the uncoupling of oxidative metabolism from ATP production[41]. Thermogenesis of the brown adipose tissue is stimulated by the the sympathetic nerve terminals in the extensive vascular and nerve supply. Uncoupled thermogenesis is highly active metabolically and predominately utilizes lipid as fuel, but may also take up glucose as well[41,42]. Activation of brown adipose tissue has anti-obesity as well as glucose- and lipid-lowering effects.

Stimulation of the sympathetic nervous system below the level of SCI is impaired in this population. Therefore, the activation of brown adipose tissue in SCI may be limited. In response to exercise, the sympathetic nervous system in able-bodied individuals releases epinephrine to initiate the process of lipolysis as a source of fuel in cellular respiration[42]. In the SCI population, this process is altered and it is thought that muscle hypertrophy may trigger lipolysis instead of epinephrine release[9,10].

Uncoupling protein in brite adipose tissue: The phenomenon known as the "browning" effect occurs when white adipose tissue begins to accumulate the uncoupling protein (UCP 1) that characterizes brown adipose tissue. This transformed white adipose tissue is referred to as brite/beige adipose tissue[41,42]. Although it possesses the UCP 1 which essentially mediates adaptive thermogenesis, it is unclear as to how effective the mitochondria with UCP 1 in beige adipose tissue are in performing thermogenesis[41,42]. This is especially significant in the medical field as a further understanding of this phenomenon could lead to new therapeutic strategies for obesity, diabetes, and other metabolic disorders. Due to the lack of sympathetic nervous system in SCI and decrease in energy expenditure, finding a therapeutic approach of transforming adipose tissue into thermogenetic cells may allow SCI individuals to decrease adipose tissue accumulation.

Pharmaceutical techniques which may activate the UCP 1 in beige adipose tissue may cause significant declines in white adipose tissue, further benefiting the metabolic profile and body composition after SCI.

SIGNIFICANCE AND FUTURE IMPLICATIONS

The rapid loss in muscle mass following SCI leads to serious metabolic consequences similar to extensive decline in basal metabolic rate (BMR), insulin resistance and impaired glucose tolerance. The evidence suggests that there is up to 22%-40% decline BMR in persons with SCI based on their level of injury and about 50%-75% suffer from impaired glucose tolerance or type II diabetes mellitus[43,44]. Dyslipidemia, as manifested by decreased level of circulating high density lipoprotein-cholesterol and increased levels of triglycerides and low density lipoprotein-cholesterol, contributes to an accelerating atheorgenic process to the cardiovascular system after SCI[4,45]. The economic impact and burden of these comorbidities may be of paramount significance to study the regional and ectopic adipose tissue changes after SCI.

The disruption in the energy balance process predisposes these individuals to become fat building machines with a fat storage capacity that exceeds more than 30% of their total body mass[23]. There are also substantial shifts in substrate utilization from reliance on fat as a source of energy to the exercised muscles to be dependent on the short-term energy supply of the glycogen storage. This is primarily impacted by the transformation of slow oxidative to fast fatigable muscle fibers[46]. Talmadge *et al*[46] estimated that by 24 wk, the vastus lateralis, gastrocnemius, and soleus muscles, approximately 90% of muscle fibers, are fast twitch fibers compared to 6 wk at baseline. The process typically manifests between 4 and 7 mo post-injury and can continue up to 70 mo post-injury before plateauing into a steady state of predominantly type IIx, fast-glycolytic twitch muscle fibers[46]. This transformation renders the skeletal muscle to be highly fatigable and susceptible to skeletal muscle damage after exercise.

Disruption in the process of lipolysis as a result of injury to the sympathetic chain may be another important factor that needs to be considered[25]. An acute bout of functional electrical stimulation cycling has failed to increase delivery of the circulating fatty acids to the exercised muscles[11]. We have shown that 12 wk of evoked resistance training using neuromuscular electrical stimulation and ankle weights resulted in decrease of IMF and VAT without changing SAT[9].

We should acknowledge that persons with SCI consume close to 40% of their dietary intake as fat; which is likely to be a major source of the continuous and longitudinal changes in body FM[9,28]. This is accompanied with low consumption (less than 20%) of dietary protein intake[9,47]. Dietary intake can be manipulated to enable more effective utilization of macronutrients[47]. The American diet is especially prone to consume

excessive carbohydrates and fats which alter blood glucose levels and increase adipose tissue if not expended. Individuals generally consume a high-fat diet that may further disrupt their metabolism. Therefore, dietary intake is equally important as an exercise after SCI. Dietary habits can be more easily manipulated and controlled than exercise intervention due to various existing exercise barriers in the SCI population[48].

Administering of pharmaceutical interventions similar to testosterone replacement may be another vehicle that can be utilized to overcome that reduced anabolic level after SCI. Using DXA to measure body composition, Bauman *et al*[49] did not observe changes in whole body and regional body FM after administration of 1 year (5-10 mg) of Testosterone replacement in hypogonadal men with chronic SCI. The study noted signifcant increase in lean mass and resting energy expenditure[49]. It is yet to be studied the long-term effects testosterone administration on ectopic adipose tissue sites and the interaction with exercise after SCI.

Individuals with SCI are limited in their physical activity to the muscle mass above the level of injury. According to guidelines generated by an expert panel, adults with SCI should engage in at least 20 min of aerobic exercise training twice weekly prescribed at moderate-vigorous intensity or 3 sets of 8-10 repetitions of resistance training to the major muscle groups[50].

Once weekly of exercise training in SCI has also shown to maintain overall body composition, combating the otherwise inevitable increase in adipose tissue characterized by this disease. Our research found that once weekly of upper extremity circuit resistance training or neuromuscular electrical stimulation did not impact body FM after SCI[51,52]. Limited transportation interferes with accessing clinical settings; home-based training may be possible to allow for training programs especially with advancing in tele-health communication similar to the video conferencing.

CONCLUSION

Different adipose tissue compartments have been highlighted in the current review. Their full contribution to the metabolic health after SCI is not fully understood. The use of sophisticated imaging techniques allow to distinguish these compartments and to quantify their changes in response to SCI and training. Different rehabilitation interventions similar to exercise, electrical stimulation, bionic suits, dietary and pharmaceutical interventions may be available; however, their effects on subcutaneous and ectopic adipose tissues are yet to be studied and their effects may be attenuated by the disruption of autonomic nervous system and limited access to these rehabilitation interventions. Strategies targeted towards skeletal muscle hypertrophy and gain in lean mass are likely to improve the basal energy expenditure, reduce adipose tissue stacking and improve metabolic profile after SCI. Therefore, individuals with SCI may require a very personalized treatment plan in a multidisciplinary approach to prevent the excessive gain of adipose tissue and loss of lean muscle mass. This interdisciplinary approach is most beneficial and may be of great benefit in attenuating the changes in whole and regional body composition after SCI.

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