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# Glucose Transporter 4, Biomarker Development and Metabolic Syndrome in the Arctic

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**Commentary**

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## Abstract

A general hindrance to research and clinical surveillance in the Arctic and sub-Arctic is the lack of early measured, supporting biomarkers for risk assessment. The increasing prevalence of visceral obesity is a risk factor for metabolic syndrome and has been associated with an increased risk for type-2 diabetes. Environmental chemical pollutant exposure can have an impact on adipose tissue function.

The common sources of exposure for metals in the Arctic are air, water and food. Metals have been reported to affect behavior of adipocytes; methyl mercury has been shown to be cytotoxic to differentiating adipocytes. This impact on differentiation suggests that GLUT-4 as a biomarker for the impairment of the insulin-signaling pathway would be a valuable tool for studying type-2 diabetes and metabolic syndrome. The Glucose transporter 4 (GLUT-4) is a widely studied biomarker in myocytes, adipocytes and more recently peripheral blood mononuclear cells (PBMC). PBMC GLUT-4 may be a good molecule for studying the impacts of mercury in different sentinel species residing in the North. GLUT-4 has been studied in both canines and humans and samples from both species can be obtained from rural Arctic communities.

**Keywords:** Metabolic Syndrome; Adipocytes; Arctic; Biomarkers; Glucose

**Abbreviations:** T2D: Type 2 Diabetes; Met S: Metabolic Syndrome; PBMC: Peripheral Blood Mononuclear Cells; GLUT-4: Glucose Transporter 4

## Introduction

Tens of thousands of industrial and personal product chemicals are in use today and distributed globally, often ending up in the Arctic. Many of these chemicals, such as mercury, have potential health risks to humans and other organisms in the environment [1-3]. Lead, mercury and cadmium are commonly used metals that have led to widespread contamination of food and water [3,4]. There is currently a scarcity of information regarding the effects of exposure to these metals on cytokine regulation when released by adipocytes as it pertains to the related syndromes of obesity and type 2 diabetes (T2D) [5,6].

Glucose homeostasis is related to insulin signaling and Glucose Transporter-4 (GLUT-4). GLUT-4 resides on small intracellular vesicles that are translocated to the plasma membrane in response to insulin and facilitate the uptake of glucose [7]. The ability to track GLUT-4 is essential to understanding whole body glucose homeostasis. GLUT-4 trafficking represents a potential early defect and contributes to insulin resistance in diabetes [8]. Studies in both humans and dogs, have demonstrated the presence of white blood cells containing GLUT-4 which suggests that measurement of GLUT-4 levels in peripheral blood mononuclear cells (PMBC) has the potential to be used as a biomarker for insulin resistance [9-12].

This creates the possibility of correlating plasma metal or persistent organic pollutants (POPs) exposure to the PBMC GLUT-4 levels, and developing a quantitative risk exposure model for T2D and Metabolic syndrome (Met S) in rural and extreme environments.

## Traditional Lifestyle

Over the past 100 years, societies in the North American Arctic and sub-Arctic have transitioned toward the "Western diet", composed primarily of highly processed 'factory foods' high in sugars, omega-6 and saturated fatty acids, and low in fiber, phytoactive compounds from fruits, and omega-3 fatty acids. This 'nutrition transition' has been identified as playing a central role in the significant development of obesity, insulin resistance, and metabolic syndrome, which in turn are major risk factors for cardiovascular disease and T2D [13-15].

The American Diabetes Association lists American Indians and Alaska Natives as one of the highest risk populations for developing T2D, with a prevalence of 16% compared with a 9 % national average [16]. However, research that focuses solely on isolated Alaska Native communities, that preserve traditional diets, report lower rates of diabetes, even though obesity rates in these populations equal or exceed the national average. Geographic isolation in Alaska and the Arctic has retained the hunter gatherer lifestyle. Alaska Natives rely on traditional diets and have a historically low prevalence of diet-related diseases [17]. The relatively low rates of diabetes among Alaska Natives are attributed to diets high in fish and berries, along with the active lifestyle that accompanies hunting and gathering of traditional foods [18]. Alaskan villagers eat on average 4.8 kg of subsistence foods per week, 60% of which are finfish such as salmon [19-21]. The traditional Alaska Native diet is higher in omega-3 fatty acids than the diet of the general US population. Many types of berries are also common in Alaska and have been shown to have positive health effects, including anti-diabetic and anti-inflammatory properties [20,22]. Seasonal harvests are major community events especially in rural Alaska communities. People commonly harvest berries of the *Vaccinium genus* (bog blueberries, lowbush cranberries, and other wild berries), when the berries are ripe in July, August and September, and use them year-round both for food and medicine [22,23]. Climate change and global transport of contaminants may place the quality of subsistence food at risk in the future [23,24].

## Dog Model

Dogs are an ideal research model for immune function, nutrition, exercise, toxicology and aging [12]. Because they possess key features associated with cognitive dysfunctions such as beta-amyloid pathology and oxidative damage, similar to that of humans, dogs are also a good model for the study of aging [11,25,26]. Dog mushing, once used primarily as a means of transportation in the North, has evolved into a popular national and international sport. Not only do dogs connect to people but this lends to diversity in climate, diet and location, providing great research opportunities. Dogs in northern climates are often exposed to the same environmental hazards as their human counterparts [25,27]. In many Alaskan villages, sled dogs are still a fundamental part of a traditional lifestyle, used for trapping, packing and transportation. Most of these communities are small settlements, established on or near rivers to facilitate travel and to gather food. Like humans, the dogs' diet in Alaska and the Arctic is often comprised of a variety of wild game and fish [24]. High Hg levels have been found in dogs , but unlike humans Hg levels in dogs have not yet been correlated with metabolic phenotypes [28-30].

Though there are species-specific pathologies associated with diabetes, dogs develop insulin dependent and independent forms of diabetes [28]. The prevalence of canine diabetes (classified into insulin deficiency diabetes group) is significantly lower than human, which could be a result of better diagnostics in humans or an increased incidence of risk factors like obesity, for humans, or both. Dogs are a proven model for biochemical research and can be an innovative model to link activity and nutrition to the physiological and immune effects seen in metabolic syndrome and related disorders [12]. Also, for the circumpolar north, racing sled dogs are excellent models for studying the impacts exercise and nutrition have on metabolic syndrome.

## Metabolic Syndrome (Met S)

Obesity has become a major worldwide public health issue and has been characteristically linked with hypertension and inflammation as risk factors for Metabolic Syndrome (Met S), a group of several medical conditions associated with developing the risks of type 2 diabetes and insulin resistance [30,32,33]. DeLong and Holloway have suggested that environmental exposure to synthetic chemicals, especially early life exposure to heavy metals, flame retardants and pesticides [28,30,31], may have a role in metabolic syndrome's recent increase. However, there is little published information regarding the effects of prenatal or early childhood exposure to metals and adult glucose homeostasis [34]. While the correlation between Hg and PBMC GLUT-4 has not yet been explored, increased Hg levels have been correlated with lower anti-oxidant levels and higher TNF (unpublished) and leukotrienes B4 [29]. If, as proposed, Met S risk increases with early life exposure to contaminants, it would be worthwhile to use GLUT-4 to examine the connection between exposure and glucose homeostasis

## GLUT-4 as a Biomarker

Biomonitoring uses biomarkers of exposure such as metal or organic pollutant, or biomarkers of effect such as the induction of an enzyme or the movement of a transport protein. Biomonitoring the effects of a stress, such as environmental exposure, provides trend data which can be used to develop optional health advice regarding food consumption and lifestyle factors. A good biomarker can detect both spatial and temporal trends.

GLUT-4 plays a key role in the pathophysiology of T2D and is up regulated in response to exercise which enhances cellular glucose transport in skeletal muscle tissue [8,9,11]. Maratou and colleagues have demonstrated the presence of GLUT-4 in white blood cells (PBMC). This mechanism appears to remain intact in individuals with insulin resistance [10,33]. Details of the mechanism are poorly understood and are challenging to study due to the invasive nature of muscle biopsy. Peripheral blood mononuclear cells (PBMC) have documented insulin-sensitive GLUT-4 activity and may serve as a proxy tissue for studying skeletal muscle GLUT-4 [35]. Recent studies indicate higher PBMC GLUT-4 levels in conditioned dogs and human athletes [11,12,35,36]. Differences in GLUT-4 levels use an easily accessible blood cell protein. The measurement of GLUT-4 provides a new biomarker for future studies with environmental stressors such as metal and pollutants.

## Conclusion

This commentary suggests the exploration of GLUT-4 from PBMC as a proxy tissue for studying GLUT-4 response to chemical stressors in individuals at risk for Met S. When concurrent monitoring of increased contaminant levels is available, a risk assessment model can be developed.

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