Lack of regular physical exercise or too much inactivity

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Purpose of review

To discuss the current data that acute periods of physical inactivity are harmful to health.

Recent findings

Bed rest prescribed for recovery from clinical conditions causes changes in thousands of mRNAs in leg muscles within days. Humans genetically more susceptible to metabolic disorders (low birth weight babies and type 2 diabetic offspring) are as, or more, susceptible to further metabolic dysfunction by the environmental perturbation of bed rest, as compared with healthy controls without these risk factors. High daily accumulations of sitting are not only associated with enhanced metabolic risk, but current findings report that increased sitting time leads to a reduction in insulin sensitivity. Reductions in walking or in ambulatory activity (lower step numbers taken by healthy humans) reduce insulin sensitivity and insulin signaling through Akt in skeletal muscle.

Summary

New findings using human models of physical inactivity (bed rest, increased sitting time, and reduced daily ambulatory activity), extend pre-existing research showing that transitioning to physical inactivity rapidly reduced metabolic health. Modern technological advances that remove standing, walking, and major limb movement initiate metabolic dysfunctions that likely play a fundamental role in the development of obesity and type 2 diabetes.

Keywords

bed rest, insulin resistance, metabolic disease, physical inactivity

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Introduction

This review is timely and relevant because an official 2008 US report of the Department of Health and Human Services concludes

> The data very strongly support an inverse association between physical activity and all-cause mortality. Active individuals – both men and women – have approximately a 30% lower risk of dying during follow-up, compared with inactive individuals. This inverse association has been observed among persons residing in the USA, as well as in other countries, older persons (aged 65 years and older), and persons of different race/ethnic groups [1].

We consider premature death the most important biomarker. Centers for Disease Control publications categorize physical inactivity as a leading cause of death [2]. The failure to have 30 min of daily physical activity increases the risk of many chronic diseases/conditions by more than 20% (range 20–60%) [metabolic syndrome, type 2 diabetes (T2D), coronary heart disease, peripheral artery disease, hypertension, stroke, dementia, depression, three site-specific cancers (colon, breast, and endometrial)] and elderly hip fractures [3].

Most US residents lead sedentary lives and do not get enough physical activity. In the USA, less than 5% of adults and only 8% of adolescents (aged 12–19 years) adhere to the recommendation for 30 and 60 min, respectively, of daily physical activity [4]. The amount of time spent doing sedentary activities, like sitting at a computer or watching TV, has also increased dramatically. Daily electronic media usage among children and adolescents was reported in 2010 to be up dramatically from 5 years earlier. Now, 8–18-year olds in the USA devote an average of 7 h and 38 min to using entertainment media across a typical day, which translates to 53 h a week [5]. Despite the above clear associations, historically, only a small number of studies have used prospective studies to determine the mechanisms by which physical inactivity increases risk for chronic disease. However, this area of research is growing as of late. This review will separately examine studies from the last year that have employed different modalities of inducing inactivity including bed

rest, increasing sitting time, or reduced ambulatory activity on outcome measures of metabolic and cardiovascular health.

Bed rest studies

Inducing bed rest in healthy young individuals provides valuable insight because it causes loss of healthy functional capacities independent of the disease/trauma process, and because it provides evidence that inactivity produces rapid and clinically significant losses of a maximal number of physiological systems. A classic example is the 1960s Dallas bed rest study in which 20 days of bed rest lowered maximal oxygen consumption and maximal stroke volume by 28 and 29%, respectively [6], staggering effects that shows how rapidly and dramatically extreme inactivity can impair functional capacities.

Short-term bed rest studies (3–10 days) have recently been used as a model to recapitulate the harmful effects of inactivity. It should be noted that bed rest is an extreme model of inactivity and does not accurately mimic the low levels of ambulatory activity that even sedentary individuals have in their daily lives. However, bed rest does elicit dramatic changes and thus provides a useful method for studying mechanisms. Bed rest studies in the last year have tested whether individuals with low birth weight (LBW) or individuals who are the offspring of parents with T2D (T2D offspring) are more susceptible to the harmful impact of short-term inactivity. It is already established that LBW or T2D offspring have increased susceptibility for abnormal glucose tolerance and T2D [7–9]; however, it was unknown whether they would respond differently to inactivity.

Alibegovic *et al.* [10•] studied the effects of 9 days of bed rest on insulin sensitivity, insulin action, and fat metabolism in healthy LBW individuals compared to healthy controls. Individuals were excluded from both groups if they had high fitness (>55 ml/min/kg $V_{O_{2max}}$). As expected, bed rest significantly reduced peripheral insulin sensitivity in both groups. However, only the LBW group experienced a statistically significant increase in hepatic insulin resistance following bed rest. The LBW had higher rates of lipolysis (corrected for fat mass) both prior to and following bed rest, leading the authors to hypothesize that this was linked to the development of hepatic insulin resistance in the LBW group. No other inactivity-induced alterations in metabolism (severe peripheral insulin resistance, compensatory increased insulin secretion, and decreases in skeletal muscle hormone-sensitive lipase) were different between the groups, directing the authors to conclude that LBW, itself, does not greatly increase the susceptibility to the harmful effects of bed rest, compared to normal individuals.

Key points

- Continuous bed rest, sitting too much, and decreased ambulatory activity produce metabolic dysfunctions.
- Bed rest causes thousands of changes in mRNA levels from skeletal muscle in the leg, including decreases in half of mRNAs in the OXPHOS pathway.
- Low birth weight or type 2 diabetic offspring have similar or greater than normal losses in metabolic function after continuous bed rest.
- Decreased frequency of breaks from sitting, as well as longer total duration of daily sitting, acutely lower insulin sensitivity which would chronically increase metabolic risk.
- Decreased ambulatory activity for 2 weeks decreases skeletal muscle insulin sensitivity and insulin signaling, reduces fitness and leg skeletal muscle mass, and increases intra-abdominal fat stores.

Hojbjerre *et al.* [11•] examined whether T2D offspring (39 ml/min per kg $V_{O_{2max}}$) had greater changes in adipose tissue metabolism compared with control participants (~43 ml/min per kg $V_{O_{2max}}$) following 10 days of bed rest. Measures of adipose tissue metabolism were performed in subcutaneous and femoral adipose tissue using microdialysis probes. The T2D offspring adipose tissue displayed greater glucose uptake rates compared with controls prior to bed rest. Bed rest decreased lipolysis and increased glucose uptake in femoral fat of both groups, whereas in subcutaneous fat, glucose uptake only increased in the control participants. Interestingly, it was also stated that the adipose tissue abnormalities found in T2D offspring were found in healthy controls after 10 days of bed rest, who had greater inactivity-induced changes than T2D offspring. As a result, the authors concluded that T2D offspring are not more susceptible to the harmful effects of inactivity on adipose metabolism.

Sonne *et al.* [12•] compared the effects of 10 days of bed rest on metabolic and vascular insulin resistance in individuals (~43 ml/min per kg $V_{O_{2max}}$ with no regular exercise), who were LBW, T2D offspring, or healthy controls. The individuals in all three groups were carefully matched for age, BMI, and prior physical activity levels. Prior to bed rest, the T2D offspring group had markedly lower whole-body peripheral insulin sensitivity than either the LBW or control groups. Moreover, at baseline, insulin did not stimulate an increase in glucose clearance or blood flow (across the arm) in the T2D offspring group, whereas insulin did stimulate these processes in the LBW and healthy control groups. Following 10 days of bed rest, whole-body insulin sensitivity was reduced in all three groups; however, the percentage decrease was statistically higher in healthy controls than the T2D

offspring group. Insulin-stimulated glucose clearance and blood flow in the arm were reduced in both controls and LBW groups following bed rest; however, there was no decrease in the T2D offspring because as already stated, they had a lack of insulin stimulation prior to bed rest. The authors concluded that the initial insulin sensitivity of the individual impacts the degree to which bed rest causes dysfunction. In contrast, a plotting of pre-bed rest insulin sensitivity vs. the change in insulin sensitivity following bed rest revealed a steeper slope in the T2D offspring compared with other groups suggesting that T2D offspring do indeed show a greater sensitivity to inactivity for that measure. Our interpretation of the data is that inactivity in the healthy group reduces some metabolic markers of physiological function down to the level that is witnessed in T2D offspring prior to bed rest, similar to what was mentioned in the previously reviewed study of adipose tissue metabolism following bed rest by Hojbjerre *et al.* [11•].

Alibegovic *et al.* [13••] also advanced the field of inactivity by studying the effects of 9 days of bed rest on mRNA changes in vastus lateralis muscle of healthy individuals who had no other known risk for developing T2D. The study was elegantly designed and included transcriptional analysis of skeletal muscle prior to and following bed rest during both basal and insulin-stimulated conditions (hyperinsulinemic–euglycemic clamp). Following bed rest, the individuals then took part in a 4-week exercise program followed by further transcriptional analysis of skeletal muscle. The overall purpose of the study was to determine whether bed rest impacted basal and insulin-stimulated expression of genes involved in the development of T2D and to also determine whether bed-rest-induced changes could be reversed by 4 weeks of exercise training. There are numerous novel findings in the article that strongly suggest inactivity is a primary player in the development of T2D. Bed rest led to reduced insulin sensitivity and the altered expression of more than 4500 genes (11% of genes on microarray). A total of 54% of genes in the OXPHOS pathway were downregulated, including peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), one master regulator of mitochondrial biogenesis. This is an important finding because previous reports have found skeletal muscle PGC-1α expression and genes under its control to be suppressed in T2D patients [14,15]. Importantly, 17% of genes altered by bed rest in the noninsulin-stimulated state were only partially normalized to pre-bed rest levels after 4 weeks of exercise retraining. We would suggest that this could imply permanent dysfunction from bed rest for the remainder of life. The analysis of insulin-stimulated skeletal muscle also revealed key findings. Despite the induction of insulin resistance in skeletal muscle following bed rest, insulin had a greater ability to upregulate gene expression in pathways for endoplasmic reticulum stress (ERS) and inflammation, pathways implicated in the development of insulin resistance and T2D [16,17]. Again, we suggest that the possibility of lifetime-enhanced susceptibility to insulin-induced activation of ERS or inflammatory pathways following bouts of extreme inactivity could increase the long-term risk of T2D. Overall, the results that short-term bed rest activates the pathways known to be upregulated in skeletal muscle of T2D patients supports the link between reduction in physical activity and increased susceptibility to T2D. We, and others, have argued for some time that the rampant increase in rates of T2D is primarily attributable to an increasingly physically inactive lifestyle [18–20].

Increasing sitting time

It is not just the total minutes spent being physically active that is important for reducing risk for early mortality and chronic diseases. The time not spent in sedentary activities like sitting is also important. The Australian Diabetes, Obesity, and Lifestyle Study have some of the earliest data showing that there was a significant direct association between sedentary time and metabolic risk, and these effects were independent of the amount of time spent in moderate-to-vigorous intensity activity [21]. A recent US report found that fewer sedentary breaks were associated with a significantly greater likelihood of metabolic syndrome [22]. These novel observations produce important challenges to existing physical activity guidelines that prescribe exercise in duration terms of days per week, rather than in frequency of avoidance of sedentary events. In some respects, the observations should have been expected based upon our 1980s work showing drastic reductions in protein (total, α-skeletal actin, and cytochrome c) synthesis rates during the first 6 h of hindlimb immobilization or suspension in rats [23–25].

A recent study by Stephens *et al.* [26•] set out to determine whether one highly sedentary day (increased sitting time) would result in reduced insulin sensitivity the next morning. The study also tested the role that energy balance (match between energy intake and expenditure) would have on this effect. On one sedentary day, the individuals consumed their normal energy intake which caused a positive energy balance, whereas on a subsequent sedentary day, the individuals were kept in energy balance by lowering their energy intake to match the reduction in energy expenditure caused by increased sitting. These two sedentary conditions were compared to a highly physical active, no sitting day. Increased sedentary time in a positive energy balance lowered insulin-stimulated glucose disappearance by 39%, whereas a 19% reduction was measured on the day in which sedentary living occurred in energy balance

(energy intake was reduced). Thus, the results show that approximately half, but not all, of the reduction in insulin sensitivity following increased sedentary time is because of a positive energy balance. Although this was an important question to test, individuals who transition to an increasingly sedentary lifestyle are unlikely to compensate by lowering their energy intake. Most sedentary individuals have to be in positive energy balance or else almost 70% of US adults would not be overweight/obese. Therefore, we believe that physical inactivity and a positive energy balance need to be studied in combination to best mimic the human condition.

Impact of reducing ambulatory activity

An early report from our collaboration with Olsen *et al.* in Pedersen's group [27] had shown a significantly increased insulin response to an oral glucose tolerance test (OGTT) by 53% and visceral fat mass by 7% at 1 and 2 weeks, respectively, after nonexercising men had transitioned to a lower amount of ambulatory physical activity (6203–1394 steps per day) [27]. This was an important study because the individuals transitioned from the normal amount of steps taken per day to the lower end of steps taken by very sedentary individuals, thus the human inactivity model developed by Pedersen more closely mimics modern living. We continued our collaboration with Krogh-Madsen in Pedersen's group [28••] to determine whether lowering daily ambulatory activity for 2 weeks would cause changes in insulin sensitivity and insulin signaling in skeletal muscle. Individuals who had high ambulatory activity, but were not regular exercisers (<2 h/week), were asked to lower their daily activity from greater than 10 000 to less than 1500 steps a day for 2 weeks. Results showed that it was skeletal muscle insulin sensitivity, and not hepatic insulin sensitivity, that was reduced by lowered ambulatory activity. We also showed that there was reduced insulin signaling to Akt in skeletal muscle. Furthermore, reduced ambulatory activity lowered $V_{O_{2max}}$ by 7% and significantly lowered lean mass in the legs by 2.8% (0.5 kg). The parallel losses of peripheral insulin sensitivity, $V_{O_{2max}}$, and leg lean mass are extremely clinically relevant as decrements in all three measures are linked to increased morbidity and mortality [29–31].

Conclusion

Bed rest rapidly induces dysfunction. Approximately 4500 mRNAs in leg muscle changed after 9 days of bed rest in healthy individuals. A total of 54% of genes in the OXPHOS pathway were downregulated, including PGC-1α, showing that inactivity can alter genes linked to mitochondrial dysfunction. Unexpectedly, 17% of the changed mRNAs did not recover with 4 weeks of exercise training after the bed rest suggesting that bed rest has lasting consequences. LBW and T2D offspring elicit many of the negative consequences such as peripheral insulin resistance after bed rest as did healthy individuals. However, LBW showed additional insulin resistance in liver. T2D offspring had lower insulin-stimulated glucose clearance and blood flow before bed rest, and thus bed rest only lowered these measures in healthy controls. Sitting is unhealthy. Both longer lengths and fewer breaks from sitting time increase metabolic risk and transitioning to a greater sedentary time for 1 day reduced insulin sensitivity significantly. Reducing daily walking is unhealthy. Reduction in daily ambulatory activity increased insulin response to an OGTT and visceral fat mass at 1 and 2 weeks, respectively. Skeletal muscle, but not liver, insulin sensitivity was decreased after 2 weeks of reduced ambulatory activity. These studies show that acute physical inactivity evokes physiological maladaptation(s) that play a fundamental role in the development of obesity and T2D. Reductions in sitting time and more walking are simple primary preventive measures to lower physical inactivity.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 415–416).

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