Chapter 6

Is Insulin Resistance Work Related?

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Additional information is available at the end of the chapter

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Abstract

Incidence of insulin resistance continues to grow, becoming a major public health concern worldwide. Besides the classical risk factors (obesity, unhealthy nutrition and lack of exercise), extensive research about some occupational hazards supports their association with insulin resistance and metabolic syndrome. On the one hand, the classical risk factors for insulin resistance are augmented by the changes of the working conditions: the occupational level of physical activity has a tendency to decrease, reducing its contribution to the overall level of physical activity and favouring a sedentary lifestyle and the occupational stress became the second most common work-related health issue, contributing to the increase of the maladaptive habits, such as unhealthy nutrition. On the other hand, some insulin resistance risk factors are primarily occupational hazards: desynchronization of the circadian rhythm and sleep disruption during the night shifts, workplace air pollution (particles, solvents), heavy metals (arsenic, mercury) or persistent organic pollutants exposure. Meantime, workplaces are excellent settings for health-promotion programmes and metabolic risk reduction, if there is managerial commitment and support. Therefore, assessment of the risk, screening and workplace intervention programmes to reduce insulin resistance incidence should be included in the occupational health service provision.

Keywords: insulin resistance, occupational stress, sleep desynchronization, night shifts, sleep duration, indoor air pollution, persistent organic pollutants arsenic, mercury

1. Introduction

Insulin resistance (IR) is a complex pathophysiological state characterized by reduced target cells responsiveness to insulin. The variety of its manifestations correspond to the complexity of insulin actions in specific tissues; the IR state reduces glucose uptake in muscle and other insulin-dependent tissues, increases lipolysis and fatty acids delivery from adipose tissue, increases hepatic glucose output and sodium retention, impairs uric acid metabolism,

enhances vascular endothelium vasoconstriction and inflammation—promoting atherosclerosis and induces a systemic low grade metabolic inflammation. Two are the major clinical consequences of the IR: the cardio-vascular disease and diabetes. There are also significant links between IR and other clinical conditions such as non-alcoholic fatty liver disease, polycystic ovary syndrome and colorectal cancer. Cardiovascular diseases are already the leading cause of death in industrialized countries [1] and diabetes prevalence has doubled between 1980 and 2014. Diabetes is estimated to become the seventh leading cause of death in 2030 [2]. Taken together, all medical conditions related to IR are responsible for a high percentage of the total mortality rate. Therefore, prevention and early diagnosis is a major public health topic.

For many years, IR has been considered a complication of obesity but a non-obese metabolic obese profile has been identified in the past few years, as up to 15–30% of the IR subjects are in the normal range value of the BMI. The complex pathogeny of IR has been explained by complementary or synergic interactions between genetic and epigenetic factors, gut microbiota and environmental factors. As the environmental factors are the modifiable ones, the intervention, including workplace interventions, became nowadays a major health prevention direction.

Insulin resistance is difficult to measure in clinical practice; therefore, surrogates are used for its assessment such as basal insulinemia, the homeostasis assessment index (HOMA-IR), glucose ratio to insulin and the glucose tolerance test. Clinical markers for IR are lipid metabolism impairment (increased triglycerides, reduced HDL cholesterol and increased LDL cholesterol), plasma uric acid increase, renal disease markers (albuminuria) and cardiovascular effects (hypertension and cardiac remodelling). As already mentioned, obesity, particularly the visceral deposition of the adipose tissue, is a risk factor. In different configurations, according to different scientific organizations, these factors define the metabolic syndrome, a more suitable clinical diagnostic. Although I fundamentally agree with those considering that metabolic syndrome is an 'artificial syndrome'—in fact is just a cluster of risk factors—and that diagnostic procedures should be developed for an easier clinical diagnostic of the IR syndrome, this article will have to rely on data accumulated under the metabolic syndrome entity, as it is much more frequently used in the medical literature.

Nutrition, lack of physical exercise are not occupational hazards that are traditionally IR risk factors. In recent research, there is more and more evidence accumulated on how particular occupational risks are involved in IR and this makes the subject of increasing interest for occupational physicians.

2. Epidemiological arguments

An impressive number of studies have emphasized that risk factors for cardiovascular and diabetes are more prevalent in low-educated, low-income population [3–8], particularly related to the high incidence of the negative health habits (smoking, drinking, high fat or low fruit diet [8]). Being a member of a low social class during childhood [9] also favoured unhealthy-related behaviours: low level of sport practice, high fat diet, emotional stress and material unfavourable conditions. In different cohorts, significant differences between men

and women [6, 7] were found, which could not be fully explained by sexual level of hormones. Marital status [5] in men appeared to have different influences in developing countries compared to the developed ones: a high risk factor in developing countries and a low risk factor in western countries [4]. The high prevalence in developing countries has been explained by cultural habits such as accessibility to eat out or practice outdoor physical activities and less concern about gaining weight. In women, marital status in western countries is associated with an increased risk.

In the early years of socio-economic development, the changing habits represent a risk factor for IR [10, 11]. The theory of epidemiological transition states that, under development conditions, there is a switch between mortality dominated by infectious diseases to mortality related to degenerative and man-made diseases [12]; conditions related to IR fill in this category, reflecting changes in nutrition and transition from physical activity to sedentariness [11]. In these countries, at the beginning of the development era, the high income class has higher risk [5], as it has access to more resources, moves to more sedentary lifestyle and tries to compensate all childhood economical disadvantages and frustrations accumulated.

Even if there are differences according to the socio-economic development period the country is passing by, there are also many similarities. For example, a comparison between Taiwan and US revealed interesting similar inflammation scores (serum IL-6, CRP, fibrinogen, sICAM-1, sE-selectin and sIL-6R), cardiovascular risk factors (systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, glycosylated haemoglobin, BMI, waist-hip ratio and resting pulse) and hypothalamic-pituitary-adrenal axis and sympathetic nervous system function (epinephrine, norepinephrine, DHEAS and urinary cortisol) in relation to the socio-economic status [13].

Occupation and employment status are major determinants of the economical welfare and unemployment has been linked to metabolic risk in both developed and in under development countries [4, 5, 14]. There is difficult to find common grounds for data reported from different countries, as occupations are differently coded and registered: an US countrywide survey found maximum incidence of risk factors in the farm industry (operators, managers and supervisors), in food preparation and food services, motor vehicle operators and among administrative staff (secretaries, stenographers and typists), and the lowest in professional specialties (particularly in writers, artists, entertainers and athletes) [15]. Several studies have classified occupations in manual (blue collars) and non-manual (white collars, office workers) activities and found either increased or a decreased incidence of metabolic syndrome components in manual workers [16, 17]. These differences were most probably related to the confounders not included in these studies, such as nutrition, smoking, alcohol and level of occupational physical activity.

There are many limitations of these epidemiological studies for a direct application in the occupational physician practice, although the prevalence and social risk factors are important. They give a broader perspective for any intervention proposed. The epidemiological transitions reflect the major trends and do not provide specific information by industry. As far as working conditions are concerned in the transitional period, the main negative factors are the unbalanced working hours to leisure activities, the increased number of jobs with sedentary activity and the increased amount of perceived stress.

3. Occupational hazards

3.1. Sedentary lifestyle

The link between inactivity and insulin resistance has been documented for many years and extensive experimental and clinical research have clarified this relationship in detail. Currently, an inactive person is defined by having less than 30 min/day of at least moderate level of activity, either as occupational or as leisure time activity. As the occupational activities become less physical demanding, it would be reasonable to compensate by more physical activities such as sports practice, gardening and brisk walking [18] instead of increasing the number of hours of TV watching or computer interactions, as we see as a trend nowadays [19]. It is estimated that only 20% of currently industrial jobs demand an average level of physical activity, with a reduction of more than 100 kcal/day in energy expenditure since 1960 [18].

Benefits of exercise in metabolic regulation: Glucose is transported into muscle cell by facilitated diffusion through GLUT4 and GLUT1 channels; GLUT4 is the major transporter. In resting conditions, GLUT4 is located intracellularly and its traffic to the membrane is insulin mediated. Inside the muscular cell, glucose is phosphorylated to glucoso-6-phosphate (G-6P), a compound that cannot transfer outside the cell. During a rest, it is stored as glycogen and during exercise it takes the glycolytic pathway. During exercise, the blood flow increases, thus increasing the amount of glucose available; this creates a gradient for glucose to entry the cell. As cells utilize energy for sustaining muscular contraction, the ratio of AMP/ATP increases, activating the AMP-activated protein kinase (AMPK). This kinase is able to enhance the transport of GLUT4 to the membrane in an independent insulin manner. AMPK activity is also increased by leptin, through indirect hypothalamic action and adiponectin, by a direct action. In obesity, resistance to leptin diminishes AMPK activity [20]. Exercise increases GLUT4 transport and fatty acid oxidation, improving insulin sensitivity. Acute changes depend on the energy balance: if this is positive, the carbohydrate oxidation will prevail and if it is negative, the fatty oxidation will be enhanced [20]. In order to reduce fatty mass, a negative balance is also requested. The type of exercise also influences the energy substrate utilization: endurance training increases fatty acid oxidation while resistance training, increases glucose uptake and utilization; most probably, this is due to the increase in muscular mass [21]. Lipoprotein lipase increases after training and maintains a higher level afterwards; the higher the level of exercise, the longer will be the duration of the high level of lipoprotein lipase and the preventive action. Chronic training contributes to increase the number of myofibrils and their oxidative capacity. Training has also a role in restoring mitochondrial content in ageing populations or in different pathological conditions [22–25] and in activating satellite cells [26]. The mitogenesis effect increased with 25% when calorie restriction was associated [27]. In previous sedentary obese men and women, training increased the mitochondrial electron transport and decreased IR.

Exercise partially counteracts other risk factors, such as a fatty diet. High lipid intake increases the fatty acids content in muscular cells, β-oxidation, acetilCoA level, NADH/NAD ratio (slowing of tricarboxylic acid cycle) and leads to citrate accumulation. Citrate inhibits muscle hexokinase and reduces the formation of glucoso-6-phosphate; the glucose traffic through

GLUT4 channels is, therefore, reduced, contributing to chronic hyperglycaemia. This processes favours fatty acid utilization and counteracts the insulin metabolic switch. A vicious pathological cycle is created between decreased sensitivity of GLUT 4 and reduced uptake of glucose. Some benefits of exercise are explained by disrupting this cycle. Training even reversed the other negative risk factors, such as obesity influence or small size at birth [28].

Relationship between sedentary lifestyle and obesity: Sedentary lifestyle infers a low energy expenditure that should be adjusted by a balanced reduction in food intake, but food intake is driven by many other factors compared to expenditure in abundant, accessible nutrient societies. In such context, calorie intake becomes easy and higher than requested for thermoregulation and metabolic purposes. In a strict mathematical formula, this will lead to increase in body weight. High calorie intake is a consequence of high fat and/or high-carbohydrate diets. Randle's hypothesis of fatty acid toxicity [29] is a classical explanation of IR induction by excessive fatty diets. High circulating level of fatty acids inactivates insulin cellular signal and impairs the switching of the metabolism from fatty acids to glucose, with progressive accumulation of intra-cytoplasmic lipids in insulin sensitive cells (including β-cells); the lipid accumulation, mainly of ceramides, induces apoptosis. In muscular cells, the increased level of fatty acids inhibits phosphorylation of insulin receptor substrate 1 and activation of phosphoinositol 3 kinase, with a decrease in glycogen storage. High carbohydrate diets, particularly of those with high glycaemic index, desensitise glucose receptors and increase oxidative stress on β-cells that ultimately lead to insulin depletion. High fructose intake feeds the gluconeogenesis and the lipogenic pathways [30] in hepatic cells and by depleting the cellular ATP content and gives to the brain a signal of energy deprivation, favouring food seeking behaviour. Increased hepatic glucose output maintains a hyper-insulinemic state with higher fat storage in adipose tissue.

Sedentary life decreases the proportion between the fat mass and the free fat mass. According to the energy balance concept, it would be expected, as the total body mass increases, that the total energy consumption increases, from the basal metabolism increase. The energy expenditure is dominated (with exception for highly competitive professional athletes) by the resting metabolic rate and the variation in size of the free fat mass that explains 60–80% of the variation in basal metabolism [31], with an approximated 5:1 ratio between free fat mass and fat mass [32]. Energy balance is a remarkable concept, but cannot fully explain the complexity of the metabolism regulation and of the metabolic flexibility, governed by insulin. In sedentary adult with positive energy balance, the proportion of fatty mass increases gradually; even if the adjusted increase of the basal metabolic rate would be proportionate with the total mass, this increase will not compensate the level of calories intake, because fat mass has lower basal metabolism than skeletal muscle and fat will continue to accumulate. Obesity, as defined by a quantitative increase of fat tissue or as proportion between fat mass and fat free mass [33], is a direct consequence. The abnormal proportion and not the BMI is, in fact, related to the metabolic risk factors. This explains, at least partially, the cardio-metabolic risk of the non-obese metabolically obese population. This increase in quantity is also associated with qualitative impairments, a phenomenon described as adiposopathy or 'sick fat' [34]. The increased level of leptin and of other inflammatory cytokines, the decreased level of adiponectin, switch of the macrophages to the M1 pattern and to a pro-inflammatory status and lower capacity of

oxidizing fat are the main characteristics of the metabolic pattern of adiposopathy. Muscle is the main consumer of glucose and fatty acids and by that, the major contributor to the lowering of glucose and of the fatty acid plasma levels; if free fat mass (mainly muscle mass) is reduced due to the sedentary lifestyle, the risk of adiposopathy increases.

Occupational level of physical activity has a general tendency to decrease. This reduction in contribution to the overall level of physical activity explains that a significant IR risk was associated with leisure time sedentary behaviour but not with occupational activity in general population [35]. However, when looking more closely, it becomes obvious that several professions are at higher risk: for example, VDU operators in call centres [36] or bus drivers [37] had a higher OR for metabolic syndrome, after confounders such as smoking or leisure time activity were excluded. Comparison of sedentary lifestyle has been highly suggestive between different professions and even among same profession that has specificities according to national regulations: for example, police officers and administrative clerks have the higher risk than fire fighters in states where training programmes are strictly supervised but not in voluntary forces (US) [38].

During work, the sedentary activity can be more sustained (more than 30 min) than during non-working hours and this has also an impact [39]. Beneficial effects in adiposity measures, triglycerides and 2-h plasma glucose were obtained even in sedentary persons with more interruptions in sedentary time [40].

Sitting for more than 1 h reduces the lipoprotein lipase activity [41] and the non-exercise activity thermogenesis [42]. Adjustable workstations might be a solution for prolonged sitting activity. In a recent systematic review, the majority of prospective studies found that occupational sitting was associated with a higher risk of diabetes and mortality and to some degree of cardiovascular risk. These apparent conflicting results between the two consequences of the IR could be related to the heterogeneity of study designs and to the inconsistency and sufficiency of data recorded on overall physical activity. Possible other confounders are diet, tobacco, alcohol and high energy food consumption, as sitting for long hours increases the chance of negative habits to develop. When the total physical activity was considered, the association between sitting and metabolic risk lost the statistical significance [43].

Clinical approach: Clinical evaluation of the physical activity is rather easy and should be part of the routine examination. BMI is also very frequently recorded and, even if it has the above-mentioned limitations, it has an orientation value. In order to be more specific about the metabolic risk, abdominal circumference could be added to the physical examination, particularly to the non-obese persons, defined by the BMI index. More accurate data about fat mass proportion are obtained by bioelectrical impedance analysis, but they are not used in routine clinical examinations.

As high physical activity has numerous benefits, it should be encouraged to everyone, according to its age, health status and preferences. There is enough evidence that even small increases, if they are sustained and become part of the routine, have high medium-term impact as primary or secondary preventive measures. If sitting is the main problem, an ergonomic intervention could be beneficial.

3.2. Sleep and night shifts

Sleep duration and sleep architecture are important indicators of individual health. When normal sleep is impaired, alertness, memory, learning, thermoregulation, respiratory, metabolic and cardio-vascular regulation are also disturbed. This broad spectrum of effects is one of the consequences of the complex connections between the hypothalamic clock and different nuclei in the central nervous system [44] and of the interaction between the central and the peripheral circadian regulators. Assessing sleep duration, sleep-wake cycle and sleep disorders in the occupational medical practice is very important, because they influence significantly the fitness for work particularly in high risk jobs for accidents (professional driving, traffic controllers, working at height, etc.).

Normal sleep regulation: Sleep onset and duration are the core elements of sleep-wake regulation. Sleep-wake regulation is currently explained by two biological models: the sleep homeostasis and the circadian clock. Sleep homeostasis refers primarily to the variation of sleep pressure, while the circadian clock concerns the activity of the hypothalamic pacemaker, acting independently of the prior sleep period [45]. Although interrelated, their regulation pathways are different: sleep pressure is mainly dependent on the existing sleep debt and is the physiological contributor to the recuperation of this debt. If during the previous day the sleep duration was shorter, the sleep homeostasis will intervene to correct the deficit.

The pacemaker of the clock automatism is genetically set to a circadian rhythm and is controlled by the environmental factors. The circadian period (the interval that covers a full cycle of sleep-wake, not influenced by external constraints) is the *tau*; *tau* varies in healthy individuals between 24 and 25 h and reflects the automatism of the suprachiasmatic nuclei processes (is circadian clock dependent). In healthy adult individuals, periodicity of sleep duration waxes and wanes ranges broadly (around 2–18 days), indicating that for a specific individual the number of hours slept varies in consecutive days, having a repetitive pattern of duration. For example, for the 5 days pattern, the number of hours slept in day 1 is the same as the one in day 6; between day 1 and day 6 there is an increase and then a decrease in duration of sleep. This inter-individual variation is determined by the different build up sleep pressure in healthy individuals and is dependent primarily to the sleep homeostasis. This variance will impact on different ways the adaptation to night shifts and to longer working hours of different individuals.

Under a certain extent, the clock is self-regulated by its genomic functionality. The activation of the hypothalamic neurons starts with the transcription of the *Clock* and *Bmal 1* genes that have circadian variations, related to day-night transitions; their products form a heterodimer (CLOCK-BMAL1) that binds to the promotion site of *Period 2* (*Per2*), *Cryptochrome* (*Cry*). The cytoplasmic levels of PER2 and CRY regulate the transcription induced by CLOCK-BMAL1 heterodimer through a negative feedback loop. Besides this auto-regulated feedback loop, *Clock* and *Bmal1* are also influenced by a secondary control loop, acting on two nuclear receptors, the *Retinoid-related orphan receptor* (*Ror*) and the *Rev-Erb receptor*. While Ror is a transcription activator, *Rev-Erb* is an inhibitor one [46]. PER and CRY reach a maximum at the normal transition from day to night maintaining the negative feedback loop of the clock and contributing to the sleep onset. BMAL1 reaches the maximum at the transition from day to night, at

waking time. In order to generate the level of BMAL1 requested for waking, ROR and REV ERB maxima occur between that of BMAL1 and PER-CRY.

Dark is the physiological stimulus of melatonin, although melatonin increases during the evening even in blind persons [47]. While its major role is to induce sleep, melatonin has also other functions such as heat loss or glutathione synthesis inducer [48]. It also influences the immune response and the glucose metabolism.

Sleep cycles have normal variation during the night: in the first part of the night, there are more non-rapid eye movement (NREM) periods than in the last part; stage 1 of sleep diminishes (in percentage time of the total cycle) in the second part of the night and stage 1 is no more present after the first 4 h of night sleep. During nightshifts or sleep interruptions, the normal sleep architecture is modified and explains the tiredness people feel, after a working night, even after an equal number of hours of recovery sleep.

Normal sleep duration: A large European study revealed significant differences between countries, related mainly to cultural habits than to environmental ones (sunlight or temperature variation) as winter and summer sleep duration showed no significant variation by country [49]. On average, adults sleep 7–7.5 h/night [50]. In adults, adjusted prevalence of short sleepers (<5–6 h/night) or long sleepers (>10 h/night) is 0.52 and 0.64%, respectively [51]. Duration of sleep is influenced by genetic, personality traits and social habits. Long sleepers had higher neuroticism scores and lower education levels than short sleepers [51, 52]. Short sleepers are more frequent in adults that have not sleep alone in their childhood, as toddlers or pre-schoolers [52]. Familial nocturnal short sleepers have been identified in a mutation on the gene *DEC2*: in persons caring this mutation, the whole duration of sleep in 24 h is less than 6 h [53]. Shorter sleeping time was associated with the total time spent sitting and with increased screen time in a large cross-sectional European survey [54], linking this risk factor with sedentary lifestyle and with a long time of computer interaction.

Metabolic effects related to sleep regulation: Hypothalamic clock does not regulate just the sleep-wake status; it is the central driver for the peripheral clocks correspondents in colon, stomach, pancreas, liver, adipose tissue and muscles: through this integration, certain metabolic pathways have circadian fluctuation. It is estimated that 10–15% of the gene transcripts have rhythmically 24-h cycles; besides the genes expression, translational changes have also circadian fluctuations. There is a normal variation of the peak transcripts during day (e.g. proteins involved in inflammation and hormonal response) or night (e.g. proteins involved in ribosomal and epigenetic processes such as methyltransferases) [55]. In twin-based genetic studies, heritability is found responsible for 33–55% of the sleep duration; interestingly, heritability influence increases when twins are living together for a longer period in their life [56].

Besides the central clock influence, there is also an intrinsic circadian variance of the metabolic genes, as response of the Clock/Bmal1 or Per 2 variation of expression. All hormones involved in glucose regulation (cortisol, catecholamine, glucagon and insulin) have circadian peaks. There is significant increase in insulin sensitivity during the early nocturnal sleep and a returning to the pre-sleep values during the late phase of the sleep [57]. In animal studies, melatonin decreases insulin and increases glucagon secretion in pancreatic cells; high insulin

levels, as reached in type II diabetes, decrease the melatonin level [58]. In humans, several genetic polymorphisms of the melatonin gene are risk factors for IR. A later rise of the morning melatonin peak is encountered in persons with the GG allele of the melatonin gene and this time corresponds to the usual timing for food intake. The later than normal melatonin raise deregulates glucose metabolism, as it counteracts the nutrient-related signals transmitted to the pancreas cells. Other genetic variants, as the *MTNR1B* gene variant, increase the number of melatonin receptors expressed by β-cells with negative impact on the insulin secretion. Subjects carrying this allele, receiving 4 mg melatonin/day, had, after 3 months of treatment, significantly less insulin secretion and were more IR than controls [59]. Possible future testing of these genomic characteristics will allow occupational physicians to distinguish the persons that will have more difficulties in adapting to working in shifts and those that are at risk of developing metabolism disturbances, including IR.

Negative influences of work schedule on insulin resistance

1. *Short sleep duration.* Short-term sleep loss could be perceived as a metabolic stressor: it increases metabolism but also the anti-oxidant capacity [60]. These adaptations are surpassed in sleep deprivation, when major disturbances in hormonal regulation occur. Glucagon and cortisol are lower after a night of sleep deprivation [61]; there is also a lower response in adrenaline to hypoglycemia, explaining both the hunger and the fatigue syndrome in the day after. The day after sleep deprivation is characterized by both autonomic symptoms (anxiety, sweating, irritability, hunger) and glycopenic symptoms: dizziness, blurred vision and difficulty in thinking. After four nights of sleep deficit, the insulin signal pathway was reduced by 30% in adipocytes [62]. Cortisol levels increase just after one night of sleep deprivation. Even if the glucose tolerance tested by I.V. glucose tolerance test was similar with the reference group, the short sleepers had a reduction by 40% of the insulin sensitivity, both in the first and in the second phases of response [63]. Another strong argument of the influence of sleep on the IR is the reduction of HOMA-IR after an increase of amount of time slept by 45 min/night, a rather cost-effective intervention for prevention of IR [64].

   The work time arrangements are very important for maintaining a physiological recovering sleep. Increased risk for metabolic syndrome was not constantly found in relation to working in shifts. However, alterations in glucose and lipid metabolism, observed in experimental settings [65, 66] of night shifts combined with a total reduction on sleeping hours (less than 5 h/day) and adverse nutritional habits [67] significantly increase the risk.

2. *Desynchronization of the circadian rhythm*. Another consequence of working in shifts is the shifted circadian rhythm (desynchronization, misalignment). The desynchronization increases the effects of sleep deprivation; the insulin sensitivity is twice reduced if restriction is combined with 8.5 sleep delay (circadian misalignment). After 10 days of longer day duration (duration of 28 h) a significant increase of glucose, decrease of leptin, reversed cortisol cycle and an increase of mean arterial pressure [68] have been recorded. A decrease in insulin sensitivity and leptin secretion are also common [69].

   The metabolic effects of the desynchronization on the circadian rhythm have been explained by the conflict between the disturbed circadian variations of the peripheral clocks

and the feeding stimulus. In general, peripheral clock shifts at a slower rate than the central clock. The circadian variation of different peripheral factors involved in metabolism regulation such as adipokines [70], pancreatic secretions, PPARγ PGC1α is supported by numerous experiments. Besides this circadian variation, their expression is also triggered by the nutrition intake. For example, leptin plasma levels depend on meal time; irregular time of nutrient intake is a risk factor for the leptin resistance, a common finding in IR [71]. Pancreatic cell possesses self-sustained circadian genes and protein oscillations of the transcription factors clock bmal1 [72]. PPARγ, a regulator of adipocyte differentiation and secretion and of insulin signal transmission, has circadian oscillations [73] but it is also activated by fatty acids. PGC1α coordinates genes in lipid and glucose metabolism, the PAI-1 promoter and the thrombocytes activation [30]. It is stimulated, in heart and liver, by fasting [74]. What are the specific interferences between the intrinsic oscillation of expression of these proteins and the environmental factors (mainly nutrition and light) are currently a subject of intense research.

Social and psychological factors are other important modifiers of sleep homeostasis and even of the pacemaker control, with specific markers at the cellular level. For example, in forced-desynchrony experiments in which the sleep-wake cycle and the associated fasting-feeding and dark-dim light cycles are scheduled at a longer *tau* than 24 h, disrupted transcription of the clock genes expression, epigenetic modifications of chromatin, impairment of the RNA polymerase, modification of the regulation of transcription and translation of heat shock proteins and temperature-sensitive RNA binding proteins (CIRBP and RBM3) have been recorded [55].

The higher weight gain of the night eating syndrome is another consequence of the desynchronization of the circadian rhythm. A plausible biological explanation is that the nutrient-induced stimulus is acting out of the phase of the physiologic oscillations of these proteins. If, for example, melatonin secretion is delayed, there will be a decrease time between wake time and circadian melatonin offset phase that will increase the eating behaviour. The modification of appetite could also be related to changes in ghrelin and leptin levels in short sleepers, significantly increasing BMI [75]. Changes in preference for salty or high carbohydrate foods, irregular meals and snaking behaviours [76] have also been reported.

3. *Sleep disruption* is well studied particularly in sleep apnea, but in this specific sleeping disorder the intermittent hypoxia was the core mechanism for the explanation of the majority of the cardio-metabolic influences.

During the night shift, sleep disruption cannot be avoided. It certainly affects the quality of sleep and the sleep architecture (the proportion between REM and NREM cycles and their duration). Sleep (particularly REM cycles) activates transfer from the short- to long-term memory and allows, from the occupational perspective, to integrate new tasks of the job; therefore, time to recovery is an important factor influencing the stress level and the employees' productivity. Response to meaningful stimuli is different during sleep: for example, a person will wake up to a lower voice stimulus while hearing his own name versus hearing someone else's name [77].

The irregular sleep-wake cycle has been associated, in an ageing population, with higher cardio-vascular risk, independent of other risk factors. The metabolic consequences of frequent sleep disruption are similar to those of sleep deprivation.

Sleep latency may become problematic after frequent disruptions of the sleep and this affects the duration of sleep after the shift, acting in synergy with the short sleep duration.

Clinical evaluation: Anamnesis should focus on the duration, difficulty in sleep initiation and on the napping habits. Complaints such as diminished intellectual performance, tiredness, loss of interest, reduced level of attention or concentration on tasks, increased number of mistakes and work accidents should always raise the awareness about a possible sleep disorder. Dangerous habits, such as smoking, alcohol and auto-medication for sleeping pills might be the clinical manifestation of the sleep problems.

In clinical practice, a *structured interview* is very helpful for all employees at risk. In general, the following items are investigated: bedtime (bedtime resistance, sleep onset delay), sleep behaviour (amount, snoring, leg movements, number of waking episodes) and morning wake up (time, self-induced, sleepiness during the day). The sleepiness level, for example, can be evaluated using different scales. The extreme chronotypes are assessed with the Horne-Östberg morningness-eveningness questionnaire [78]. The major items used in this questionnaire are: time of getting up and of going to bed, level of alertness, the best interval during the day for occupational or recreational activities and the perceived difficulty to perform a certain activity at different hours. *A sleep diary* for a minimum 2 weeks is a very good tool for monitoring sleep duration, day or night distribution, weekly distribution, onset and wake up time. The non-recuperated sleep debt might be the underlying cause of the complaints.

Determination of the specific sleep pattern (periodicity of sleep duration waxes and wanes) would be ideal for pacing the shifts. The *maintenance wakefulness test* is sometimes necessary to assess the ability to stay awake in soporific conditions (quietness, dim light, confortable temperature). It is measured using the polysomnography method under standard conditions [79] and is an objective measure of the inability of some patients to maintain normal alertness during the daytime.

The first step in any sleep disorder without organic substrates is to eliminate contextual factors for the sleep latency or delayed sleep onset. Sometimes, just social adjustments or introduction of the basic recommendations for an efficient sleep routine will be enough (relaxing activities 1/2 h before going to sleep, avoid TV, computer screen light, avoid intense physical activities 3 h before going to bed, avoid caffeine containing beverages in the second part of the day, etc.). In other cases, avoiding shift work become mandatory, at least for a certain period of time, enough for recovery.

A special issue is related to the existing diabetes or cardio-vascular disease that might be aggravated by this working schedule. In some countries, national regulations allow the occupational physician to demand the employer another kind of working time. Whenever this is possible, it seems to be the best option.

3.3. Stress

There are many *definitions of stress*. From the biological perspective, the process underlying stress is initiated by stressors and implies a stress-response (bodily reaction to stress, both psychological and physical) that also creates an emotional impact. If this impact is emotionally positive, the perception is of a positive or motivational stress; the negative emotional

impact defines the distress. In response to chronic stressor stimulation, activation of the hypothalamic-pituitary-adrenal axis and of the sympathetic nervous system increases cortisol and adrenaline systemic levels, heart rate and blood pressure. These biological effects have been used to measure, objectively, the level of stress. Chronic high levels of counter regulatory hormones (cortisol and adrenaline) are a plausible biological explanation of the insulin resistance related to stress. Indeed, in individuals with metabolic syndrome, levels of cortisol metabolites and catecholamine are found significantly higher than in controls, with a reduced cardiac frequency variability related to the higher sympathetic tonus, and high levels of inflammatory markers (protein C and IL6); the psychosocial factors are estimated to explain around 13% of these effects [80]. Negative emotions have an acute impact on the inflammatory and vasoconstrictor tonus; an interesting comparison between acute myocardial infarction precipitated by a stressful event and the ones without a distinguished negative event showed a significantly higher monocyte chemoattractant protein-1 (MCP-1) and endothelin-1 (ET-1) in the first group [81]. Distress also influences the spontaneous individual strategies to cope with stress, leading to unhealthy behaviours such as smoking, bad nutrition, low physical activity and addictions [82].

Occupational stress is considered the second most common work-related health problem, affecting 28–40% of the workforce [83, 84]. Several conceptual models have been developed to analyse the level of occupational stress. The theory of Karasek et al. based on the job demand and the control power or autonomy [85] focuses mainly on the personal control and short-term stressors. Siegrist et al. [86] created a model based on the effort -reward balance, with more emphasis on social equity and on long-term perspective [87]. A third model, the job demand-resources model, has been proposed by Bakker and Demerouti [88], challenging previous approaches for treating the diverse working conditions in a similar and general way; this model considers that even if job demands are relatively high, they will not generate distress if the organization provides the functional frame for achieving the goals, reducing by that the physical and psychological cost of the employee. Even if there are certain overlaps in these models, their focuses are different: while the Karasek et al.'s model focuses on the psychobiological impact on the threatened control, Siegrist et al. changed the accent on the threatened reward and Bakker and Demerouti have highlighted the threatened support.

In clinical research and practice, the measurement instrument of the perceived stress is the questionnaire. Depending on the conceptual model used, the items are different: for the first model, the quantity of work, the time constraints, the autonomy in making decisions, including the creativity and the possibility of skills development are the main items. The effort-reward model uses questions to assess the time constraint, the responsibility, competitiveness and fairness of treatment inside the organization, the job promotion perspectives, respect and esteem, job status, security of employment and external motivators (adequate salary). The demand-resource model claims a specific analysis by the type of activity and organization resources and hence, there is no a general questionnaire proposed. These instruments have been enriched, in certain studies, with specific items related to sleep disorders, fatigue, sufficiency of recovery time, and posttraumatic stress (the psychological injury risk indicator) [89], and they continue to evolve, creating much difficulty in the comparison of data.

Occupational stress is closely related to job dissatisfaction. Job satisfaction has a multitude of determinants, from job content, to values and leadership of the organization, management style (participative or authorship) and organizational culture (supportive or punitive, leadership role model, carrier paths definition, co-worker support, salary benefits, recognition, work-life balance, etc.). Nowadays, when competitiveness demands frequent improvements in the organization, proper change management processes became increasingly important in maintenance of the job satisfaction. Change is stressful if there is not enough planning, supportive leadership and if it is very frequent, creating the feeling of instability [90]. It is the management duty to find possibilities for job enrichment, job enlargement or job rotation in the process of change to increase the internal motivation and the meaningfulness of the job. But the rapid development of work and constant training create high pressure on employees and reduce family and recovery/recreational time, no matter how motivated the employee is. It can be only partially compensated, sometimes, by a perceived increase of the quality of family time through the actualization of the new skills in different social contexts.

Employees quit managers, not companies but they also leave if there is a misfit between their competencies and skills and the tasks and goals requested (poor recruitment process), if there is role ambiguity or too little decision power. Work time arrangements have several aspects in which the management of the organization can intervene to reduce stress and to increase job satisfaction and productivity such as shift work scheduling, number and flexibility of the work hours and overtime. By simply forward-rotating the shift system, the mean number of days on which the workers reported sleepiness, the heart rate at rest and the systolic blood pressure decreased significantly [91]. Longer working hours lead to increase in smoking, drinking and weight gain [92], affect the need to recovery time and create psychological distress [93]. The *Karoshi* phenomenon (‘death from overwork', in Japanese, associated with more than 60 h/work month) is rarely recognized as such in western societies [94], but the silent, progressive association between insulin resistance and stress might be, interpreted, in fact, as part of the same picture.

Particularly in services, flexibility in both time and location is a new way of working that shifts the organization from standard, repetitive procedures to project-based short-term activities. In certain developed countries, such as Sweden, only 16% of jobs are regulated in terms of time, space, process flow and coordination, performance evaluation and peer interrelation, with differences between private (more flexibility) and public sectors, activity domains (services more than production) and gender: women more frequently employed in positions with higher levels of regulation than men [95]. Flexibility has certain advantages for stress reduction: it fulfils the need for autonomy and decision empowerment and gives the employee the perception of the self-determination of his working time, in terms of duration and daytime distribution. On the other hand, flexibility creates an opportunity for the employee to stay in a permanent ‘switch on’ work activity, predisposes to isolation, lack of supervision and peer support and reduces the development of the interpersonal skills and relations. These can lead to burnout or to unhealthy behaviours (e.g. snaking, increase consumption of sweet beverages, smoking) [96]. Family working balance is more and more important in dual-career couple societies and effort recovery time and psychological detachment from work are central in maintaining this equilibrium.

Relationship between IR and occupational stress: To answer this question, a comprehensive systematic review [97] of the prospective studies linking stress and metabolic syndrome found a positive relation. Gender seems to be important in terms of stressors: for women, the main risk factor was job strain, whereas for men the feeling of justice at work was the main protective factor. When assessing the individual components of the metabolic syndrome, weight gain was inconstantly associated with job stress, but low justice at work was associated with high triglycerides in men and job strain with high cholesterol in both sexes. Development of diabetes in men was in direct relation with higher demands. Job insecurity and low feeling of justice in men and effort-reward imbalance in women were associated with an increased high blood pressure risk. Low effort and low engagement lead to increased dissatisfaction towards job and in medium term might lead to a certain degree of depression. At the opposite end, the low effort and low engagement are overcommitment and this attitude also amplifies the adverse health effects; overcommitment is expressed by a continuous thinking of work during the normal social/relaxing time, with an impossible switch off from work. From psychological perspective, it underlies the need for approval and recognition at work [98]. The most frequent manifestations of overcommitment are burn out, psychological distress, musculoskeletal complaints and self-rated poor health [99, 100]. In a large Dutch study, overcommitment increased by more than 20 times the risk of emotional exhaustion in workers recording an imbalance between effort and reward compared to those without overcommitment [101].

Direct life-threatening jobs (policemen, firefighters, sailors) are well-known stressing conditions. Policemen has a high score in demand-control-support scale and in the effort-reward imbalance scale and these scores could explain the more than doubled OR of metabolic syndrome, particularly for the hypertriglyceridemia component [102, 103]. Working in confined spaces is another well-recognized stressor: after only 5 months of sailing around the world, in a rather small ship with only 16 persons an equipage, BMI, HbA1C, basal insulinemia and triglyceride level [104] significantly increased. In these particular working conditions, the circadian rhythm modification, the changing working environment, the rapidity in decision process, the loss of control on own private life and private activities and the anxiety in front of unknown future conditions were considered as additional stressors.

But occupational stress does not require only extreme conditions. A large British study, including more than 10,000 civil servants, using the demand control evaluation method in repetitive measurements, concluded that more than 14 years of chronic stress exposure increases the risk of metabolic syndrome by two in men and by five in women [105].

If job might be stressful, nevertheless loosing job or job insecurity is another very stressful event. This association is supported by many studies [106–108]. Moreover, the relationship between the numbers of financial negative events in one's life was independently related to insulin resistance in a large, general population study in Finland [109].

Health risk factors (smoking, drinking, low physical activity, increased BMI) are more frequent in public sector employees perceiving low rewards or low occupational effort [89]. While low-reward perception is intuitively link with dissatisfaction, low effort should be expected to generate the opposite; however, in a large-scale meta-analysis, it has been found that low effort and low engagement reduce the job satisfaction and increase the level

of depression [110]. These occupational stressors generate coping behaviours for the job in satisfaction and depression. However, in both prospective and cross-sectional studies, the strength of the association could be minimized by the variety of individual reactions to stress, reducing the statistical significance for each behaviour.

Stress and nutrition relationship: As nutrition is so important in the insulin resistance physiopathology, the effect of stress on eating behaviours has been largely studied. In an ideal homeostatic balance, appetite and eating should be driven by the internal eating cues (hunger and satiety). But food is also a basic primary reward and in our food abundant modern society, numerous other external factors trigger eating. Emotional food choices are certainly influenced by the level of the stress hormones; other factors, such as gender, age and cultural modulates this behaviour. Female tends to be influenced more by the negative emotions. For example, in young women, binge eating has been related to executive function impairment such as cognitive impulsivity, insufficient planning and higher levels of cortisol release in relation to stressors. The tendency towards depression is also high among them [111]. On the contrary, men are increasing their portions, when experiencing positive emotions [112].

Stressed students and adolescents generally eat less healthy [113], and this attitude is also more influenced by negative emotions [33]; body image is the main concern [114] at this age that opposes the emotional food intake. Adults may improve emotion control and, in general, increase the health concerns about food; in this context, in healthy subjects, the positive emotions become more powerful in leading eating behaviour. Apparently, even liking for specific taste changes with age: salt liking increases and sweet taste decreases [115]. Emotional eating is frequently related to sweat taste liking that is more expressed in women [115, 116].

Stress and eating dysregulation or a poor differentiation between internal eating cues (hunger, hypoglycaemia) and external stressors are closely related and may be expressed in different personalities either as overeating or as fasting. Eating dysregulation is more frequent in persons having difficulties of identification own feelings and emotions (alexithymia) [117]. High-caloric foods (snacks) are convenient food for this type of behaviour; indeed, in experimental induced stress, people often consume more sweet fat foods than usually [118]. There is a biological explanation of this consumption, as such foods increase the serotonin level that improves mood. The mood improvement creates a positive, but medium- and long-term unhealthy, feedback loop, that contributes to permanentize the behaviour. Emotional eating has been explained by inadequate parenting practices during childhood: an increase control and restriction of certain foods for fear of weight gain (the 'dietary restraint model') or usage of foods to emotionally comfort ('affective state model') are influencing the adult emotional eating and create a significant role for the food-reward behaviour in adults [119]. Recent studies highlighted the genetic role: an increased number of central dopaminergic receptor 2 and a melatonin receptor allele are a risk factor for emotional eating and energy intake under stressful conditions [120, 121].

Even if link between stress and insulin resistance seems to be well argued by the existing data, some limitations of these studies should be highlighted. The comparability and reproducibility of data are difficult because there are a variety of instruments used to measure stress. Another limitation is that most of these studies (particularly the large ones) are studies

from the public sector, and might not be fully transposed into the private sector, where competitiveness might be higher and job employment less predictable. Even less is known about small or family enterprises that have specificities in organization, human interrelation and high interference between family and occupational stress. Personal (non-published) experience with local small-medium size firms showed that where there is tendency of preferred employment of relatives, there are additional stress factors, work inequities and general level of stress perception inside a firm.

Fortunately we still have large prospective studies confirming the risk between different components of the metabolic syndrome and stress perception. Even so, the methodology of these studies could be challenged: in many studies, there is no follow-up of the drop off (quitting the job, for example, because of the high stress, weather there is a job demand/job control induced distress or an effort-reward imbalance). If we would have the methodology to estimate in a proper way the healthy worker effect maybe the risk will be even higher, but this a common bias with all occupational risk hazards. When assessing the nutritional effect of job stress, almost all studies examined the increased in BMI and none have considered or measured the dual effect of job stress on increasing or decreasing weight. Hence, we cannot conclude whereas this would influence or not the final result.

Clinical approach: There are many types of questionnaires used to evaluate the level of stress. Selecting the most suitable instrument for an organization is sometimes difficult and involvement of psychologists and human resources specialists might be of great help. In individual assessment, the detailed anamnesis, the working time and the perceived complexity of job demands are more easily revealed during the consultation. As in other occupational medicine consultations, attention should be paid to repetitive group complaints that underline a common organizational problem. Collaboration with the line managers and human resource management in a stress reduction programme is essential.

Health status also influences the employment choice and the occupational specialist has a role in modulating this choice. For example, fatigue is one of the reasons people quit shift work and organic causes should not be omitted before claiming stress as the causative factor. Clinical examination and exchange of medical information with the general practitioner are beneficial in finding the best possible solution for the employee.

3.4. Chemical hazards and air pollution

Assessing the health impact of toxic exposure is an important part of the occupational medicine practice. During the past decades, industrial exposure to chemicals has been gradually reduced in many countries by better safety measures, but low level constant and long-term exposure are still a matter of concern for many industrial and service workplaces. Occupational exposure to heavy metals occurs in many industries not only in the metal industry (mainly from electric air furnace or welding), metal refineries, battery production, colorant and pigment industries, smelter operations, radiator repair shops, mining, construction, but also in the modern days in the recycling industry and copying machine chambers. Indoor pollution and environmental exposure (from drinking water, outdoor pollution) are other possible sources of particles and chemical exposure linked to insulin resistance.

Heavy metals: Numerous studies indicated an association between heavy metals and insulin resistance (cardio-vascular diseases and diabetes) [122–127] explained by their direct effects on ROS production and inflammatory mediated cellular and systemic damage, decreased mitochondrial function with reduction of the capacity for fatty acid oxidation, inhibition of lipoprotein lipase in adipocytes and β-cells destruction [128]. Maternal gestational diabetes is also increased by heavy metal exposure [129].

Arsenic is well known for its carcinogenic, skin and neurological action. Arsenic epidemiological data about diabetes and cardio-vascular effects is quite extensive and comes from very different countries, both developed and under developed ones [130, 131]. Industrial activity and drinking water are the major source of exposure [132]. In drinking water, levels higher than 150 mg/L are positively associated with diabetes. Lower drinking water levels gave contradictory results [133, 134] in different studies, most probably needing a longer term exposure to produce the negative health effects. Arsenic is a highly reactive metal. Inside hepatocytes, the methylation of arsenate and arsenite generates monomethylarsonate (MMA) and dimethylarsinate (DMA), the latter being less reactive and more rapidly eliminated in urine. Metabolomics techniques revealed 103 urinary and 32 plasma metabolites associated with the urinary arsenic level. Interestingly, metabolites related to energy (ATP) production were common in diabetes and non-diabetes individuals, although the energy generation is different at the cellular level, insulin is active or if there is an IR. There were also other compounds affecting the citric acid cycle or the amino acid metabolism that were specifically modified only in diabetes, supporting the influence of arsenic on the diabetes status [135]. Under moderate environmental arsenic exposure [136], high inorganic urinary As and urinary DMA excretion were associated with high diabetes incidence; higher MMA had an inverse effect. Experimental data also supports an action of DMA on adipocytes (reduction of the insulin signal) and on beta cells apoptosis. Exposure burden, the type of arsenic compounds but also polymorphisms of arsenic (III) methyltransferase gene (*AS3MT*) [137] are relevant for the relation between MMA and DMA and nutrition, particularly on folate intake.

In animal experiments, arsenic has many pathophysiological effects related to insulin resistance: it reduces the intracellular insulin signal by suppressing the expression and phosphorylation of protein kinase B (PKB/Akt) and by direct inhibition of the Akt pathway [138]. Arsenic affects hepatic glucose output, increasing gluconeogenesis and up-regulates genes involved in oxidative and inflammation processes. As other heavy metals, arsenic causes mitochondrial toxicity reflected by the decreased level of the mitochondrial deacetylase, of FOXO 3a, ionic transport and membrane potential, decreased activity of manganese superoxide dismutase and increased reactive oxygen species [139]. Arsenic activates stress sensitive signalling pathways initiating pancreatic cell apoptosis [140] and oxidative stress in liver cells [141]. Arsenic has also a pro-thrombotic action and acceleration of atherosclerosis explaining the cardio-vascular effects [142, 143].

Mercury (Hg): Cross-sectional and prospective studies showing increases prevalence of diabetes [144, 145] in people exposed to Hg, which are not confirmed by others [146]. Hg is a very reactive metal: it interacts with the -SH groups of different enzymes, antioxidants

(glutathione), and even with amino acids. Substantial experimental data concluded that Hg has both direct pro-oxidant effects and a capacity to reduce the antioxidant defence mechanism [147]. These characteristics have been confirmed in high occupational exposure [148, 149]. Hg reduces gluthatione, superoxide dismutase, catalase and thioredoxin reductase [150]. Denaturation of proteins increases the endoplasmic reticulum stress, initiating apoptosis. The inflammatory status is materialized by the increased levels of IL4, IL6, IL7 and TNFα and IFNγ [150]. Apart from these systemic effects, Hg has also more specific effects related to IR development: Hg has a direct toxic, pro-apoptotic effect on β-cells [151]; it decreases the insulin effects [152] and induces apoptosis in adipocytes.

Other heavy metals have also been involved in metabolic inflammation. During the cellular immune response, it was demonstrated that radicals induced by lead (Pb) disrupt the transcription signalling pathway mediated by the mitogen-activated protein kinase, nickel (Ni) induces the NLRP3-ASC-caspase 1 and As induces tyrosine kinase Src. The nuclear factor kB is activated by Pb, Ni or Hg with an increase in gene transcription for early inflammatory cytokines, such as Interleukin 1, interleukin 6 and tumour necrosis factor. Some metals, such as cadmium (Cd), can activate an inflammatory response through tissue damage induction mediated by free radicals, which results in leukocyte recruitment and cytokine secretions. Inflammation generated by metals can be reduced by metallothionein that has the ability to scavenge free radicals and bind toxic metals through the release of Zn and oxidation of SH groups [153].

From my previous personal clinical experience, in the Occupational Medicine Clinic of the Colentina University Hospital in Bucharest, I can confirm that workers from a lead battery factory, currently closed, admitted with saturnine colic, that had heavy Pb exposure, presented almost constantly a reversible hypertension syndrome.

Heavy metals and smoking: Smoking habit is one of the most important sources of cadmium in the general population. In fact, reduction of cadmium levels in the general population has been attributed to the efficiency of the anti-tobacco campaigns and policies [154]. Lead, nickel and chromium are also found in the tobacco smoke at significant levels. The relationship between smoking and diabetes is grounded on large epidemiological studies [155, 156]. Mechanisms such as impaired peripheral glucose uptake, oxidative stress, metabolic inflammation [157], and retention of the inhaled high concentration of metals (As, Al, Cd, Ni, Hg and Pb) [158, 159] have been described. A synergic effect of occupational exposure and smoking was found in smelters [160] or mining workers [159]; the common proposed pathological mechanism is the reduction of the anti-oxidative defence [160] or the increased retention of the heavy metals.

Other toxicants: Epidemiological studies brought the attention on other environmental toxicants such as persistent organic pollutants (POP), endocrine disruptors, or substances involved in the toxic oil syndrome (presumably aniline). POP is a generic term for a variety of chloride or bromide compounds, including pesticides and dioxin. Longitudinal studies showed that persons with high basal level of blood POP are at increased risk for diabetes. Studies that have also monitored the PCB were able to exclude the non-reverse effect of

diabetes [161]. The stronger evidence of these associations came from occupational exposure studies: high accidental environment contamination [162] increased the relative risk of diabetes and of cardiovascular disease. Non-accidental occupational exposure in cohorts from 12 different countries also confirmed the relationship [163]. Bisphenol A is also a POP, well known for its endocrine disruptor effects; besides other negative effects, the rate of gestational diabetes is increased in women with a higher blood level [164]. Toxic oil syndrome-registered patients have threefold increase in prevalence of diabetes, and higher incidence of metabolic syndrome [165, 166].

The intimate mechanism of these associations is not completely found and most probably has certain specificities according to the particular substance. Many pathological pathways have been implicated: the increased accumulation of abdominal fat [167], inflammatory markers [168], adipocyte cytokines, TNFα and nuclear transcription factor kappa B (NFκB) [47], uric acid [169]. As a direct effect on the insulin signal, in animal experiments, perfluorooctane sulfonate inhibits the insulin Akt, signal leading to insulin resistance [170].

Particulate exposure: Air pollution, particularly fine and ultrafine particles, has been related to the acute incidence of cardio-vascular events and asthma attacks from inflammatory, oxidative mechanisms and pro-thrombotic mechanisms activation [171]. This correlation remained consistent after exclusion of possible confounders (education level, work exposure, alcohol, vegetable and fruit consumption, smoking or physical activity) [172]. Initially described for cardiovascular effects [171, 173], the particulate exposure includes now also the increased risk for diabetes [174, 175] and for non-alcoholic steatohepatitis [176]. Particulate matter (PM) is generally a subject of environmental health, and exposure during the day is very variable depending the microenvironment (home, kitchen, policy of smoking indoor, traffic, general level of city pollution control, occupation) [177]. However, there are also many workplaces were PM10 (the respirable component), PM2.5 (fine particles) and the PM0.1 (ultrafine particles) have still high values. Road transport, energy production and distribution, waste as well as domestic exposure (cooking) are major sources in Europe [178]. Photocopiers centres, sick buildings might also have PM10 and PM2.5 above than permissible levels.

Large cohort studies in North America showed that a 10 g/mm^3 increase in PM2.5 was associated with 13% increases in hypertension and with 18% increase in diabetes-related mortality, concluding that current PM 2.5 US standards are too high for the long-term exposure and should be reduced [179].

In different countries or regions, the proportion and the composition of air pollution differ; in a China study, fine particles bound polycyclic aromatic hydrocarbons (PAH) and this characteristic might have a cumulative effect on IR, as it has independently associated with this risk [180]. PAH is an environmental pollutant but exposure is increased in occupations that involve bitumen and asphalt manipulation, in foundries, distilleries, painting industry and other manufactories [181, 182]. Firefighters are also exposed to significant levels. Smoking is another important PAH source and, therefore, efforts to reduce this habit in workers occupationally exposed are highly recommended.

The particulate matters IR pathophysiologic mechanisms are rather similar to the ones involved in heavy metal exposure: obesity risk increase [183], enhancement of inflammation, with higher plasma levels IL8, ICAM-1 or eosinophilic cationic protein [184], endoplasmic reticulum stress and insulin signalling interference in a dose-response manner [172]. Reduction in antioxidant defence is supported by both experimental on cell lines and from the increased effect on persons with GSTM1 null alleles [184]. Disruption of metabolic genes has also been reported [185]. Several studies proposed a link between genetic variants of ABO locus; particulate exposure and IR risk [186]. When occupational exposure to particles (particularly to asbestos, welding fumes, respiratory irritants) was added to the epidemiological model, the risk of group O subjects was enhanced [187]. There is no conclusive explanation about this association, but ABO antigens are expressed also on the von Willebrand factor, presumably increasing the prothrombotic and chronic inflammation risk [188] and the ABO locus is related to the E-selectin, ICAM-1 and TNF-α blood level [186].

Cardio-vascular and ECG modifications: Controlled particulate exposure showed high systolic [189] (or high systolic and diastolic increase [172] according to the type of particle), decreased of blood plasminogen and thrombomodulin, and an increase in the inflammatory markers: CRP and serum amyloid [190]. Diesel exhaust double-blind experiment mean peak effect on systolic blood pressure increases between 30 and 60 min. after exposure and remained high 24 h after, independent of metabolic syndrome previously existing components. Interestingly, in this experiment, the increase in blood pressure was not related to perception of exposure [189]. Persons with metabolic syndrome exposed to ultrafine particles and GSTM1 null allele are particularly at risk of altered repolarization and increased QT duration [191].

Clinical approach: Indoor air pollution measurement is part of the occupational safety procedures and whenever data are available there should be transmitted to the occupational physician. The detailed occupational anamnesis, symptoms, clinical examination and existing exposure indicators orient the medical conduct.

For heavy metals exposure, biological monitoring is recommended in workplaces or occupations at risk. The biological monitoring is included in the national recommendations for occupational medicine practice in many countries. The limit values of the exposure indicators are defined for chronic poisoning. On what concerns the metabolic risk, there is no threshold limit established yet and general population data suggest that lower limits than those for chronic poisoning would be a reasonable approach. We cannot conclude this topic, until well-designed studies to address this specific objective are conducted. On the other hand, until these studies are available and taken into consideration the increasing incidence of insulin resistance worldwide, efforts to reduce this non-classical risk factor should not be postponed.

A special concern is related to the maternal and foetal risk and to the gestational diabetes. Ideally, pregnant women should not be exposed to chemicals; if environmental contamination is not easy to avoid, at least the occupational one should be limited. Besides the negative effects of chemicals on the foetus development, the increased risk of gestational diabetes adds unfavourable short- and long-term consequences.

4. Workplace interventions

As insulin resistance implication is better understood, and its prevalence increases worldwide, the number of interventions that have been published in last decade has also increased. Most of them, even if they directly target insulin resistance are better known as workplace wellness programmes. In countries were private insurance is paid by the employer, they could be a mean to reduce the insurance plans; in others, where work-promotion activities are more and more valued by the companies, they are conducted either as a channel to encourage individuals to take preventive measures through education and screening or as employment-based activity to promote health behaviours and disease management, such as stress management, adjustable work station to reduce continuous sitting, team support groups and cafeteria/canteen provision of healthy food initiatives. Although very diverse, there are however some general characteristics of these interventions:

1. *Assessment of the health risk according to the working conditions*. Risk assessment is always the first step as the intervention has to be meaningful for the organization and should reflect the specific issues of the employees. Working conditions and health-related habits should be analysed, as multi-component interventions have given better results [160]. Sometimes, just screening programmes initiated inside the company increase awareness and initiate individual actions [161]. In works with high aerobic workload, a low cardiovascular fitness is a physical risk factor and a stressor. Increasing the aerobic fitness by initiating an exercise training programme was able to decrease the basal heart rate, the BMI and the inflammatory markers (high sensitivity protein C), to increase work efficiency and to reduce stress related to work overload. Sedentary behaviour has benefited from different ergonomically interventions [162, 163]. Some studies have emphasized the benefit of sitting interruption during the working day; efficiency of short 1–2 min every half hour of sitting break was better in terms of metabolic syndrome criteria compared to the two 15 min breaks per workday [164]. In certain circumstances, cumulative risk factors are encountered: for example, seafarers are recognized as a profession with high incidence of metabolic syndrome. An intervention including healthy cooking training for ship cooks together with improvement of the ships fitness facilities and education (anti-smoking, individual exercise, extra health checks) led to a decrease in sugar intake, increased physical fitness scores and a significantly decrease in prevalence of the metabolic syndrome [165, 166].
2. *Obtaining the maximum support of the management team*. These interventions are changing behaviour interventions; they imply not only financial cost but also time allocation, organizational changes, etc. If management is not convinced and does not actively supports the programme, making it part of the organizational culture, the chance of achieving the proposed results is considerably reduced. Presenteeism, defined as being present at work, but with a limited performance in some aspects of job related a health problem, is often a high hidden cost for employers. Improving the general health status and well-being of their employees could be, therefore, perceived as a valuable investment. Stress management programmes, in particular, need specific organizational behaviour assessment and

a proactive participation of the line and human resource management. Of course, there are some universally interventions for mental health [167], but they should be aligned with other managerial and organizational initiatives [168].

3. *Proper preparation and communication inside the company*: Ideally, some representatives of the beneficiaries should be involved in preparation of the intervention, for presenting their needs and for choosing from different possibilities of implementation the best suited for them. Communication of the aim, the means and the expected results is necessary before, during and after the intervention. It is reasonable to consider that employees are in different stages of motivation for change. Therefore, stage-based intervention for non-intenders, intenders and actors (people who have already taken action towards changing behaviour) could be more effective [169, 170]. Barriers to adherence and completion of the programme are better solved in a participatory approach [171].

4. *Adapted tools*: There is no one solution for all organizations. For some, the online support is possible and is part of their working culture; in other organizations, group or individual discussions are more effective. Computer-based interventions have a better reach, particularly in larger organizations. A Cochrane systematic review on interactive computer-based interventions for weight loss or weight maintenance in overweight or obese people found that such interventions significantly reduced body weight [172]. Combined systems with face-to-face and computer/telephone interactions are also used.

5. *Team work*, from the first steps of design until results evaluation. Nobody can expect that a transformational change can be proposed and delivered solely by the occupational physician, but it is desirable that he is an active member of the team [173]; psychologists, ergonomists, nutritionists, exercise trainers, IT and communication specialists, etc. are needed, according to the scope of the intervention. Concerning risk reduction of the metabolic risk, nutrition is a traditional risk factor for insulin resistance and trained dieticians should be involved. Nutrition knowledge make people less likely to be hypertensive compared to one with low level of healthy nutrition [174] and when combined with a physical activity programmes [175], and facilitated access to healthy food, become more effective [176]. Workplaces are excellent settings for health promotion programmes, joining all these conditions together, if there is managerial commitment and support.

5. Conclusions

The minimum requirements for a health issue to become an occupational medicine subject are a proven relation with the working conditions, and a benefit from a working place intervention. This chapter had provided arguments that insulin resistance has both characteristics. It has, however, a specificity, that in some countries had brought benefits for including it in the occupational services and in others have been an obstacle: insulin resistance shares both elements of the classical health protection and of the health promotion activities.

In terms of health protection, insulin resistance is related to medium or even low exposure to air pollution (particles, solvents) or heavy metals. The biological monitoring reference for insulin resistance is not yet defined, making difficulties in interpreting field data. Using the general population assessments might be a solution, but there is clearly a need for well-designed research in this area to reach a valid conclusion. Insulin resistance is also related to other work hazards: work schedules, sedentary behaviour and stress. Concerning the work schedules, we benefit of many data, experience and general recommendations about working on shifts; flexible working time is a new challenge and probably needs more individual solutions. Occupational stress is recognized as one of the most important risk factor of the modern society and, even if it is more in the occupational psychology field, it has to be integrated in the occupational medicine service, as many other medical conditions, except insulin resistance, are aggravated by stress.

In terms of health promotion, prevention of insulin resistance and its major consequences (the cardio-vascular disease and type-2 diabetes) are perceived as part of the healthy life-style and well-being programmes. Healthy nutrition, smoking cessation, physical activity and sleep hygiene are the pillars of these programmes. The appropriate and culturally adapted design increases the adherence to these programmes; their real success is the integration of the healthy behaviours and the reduction of obesity and insulin resistance-related mortality. Management support is needed in the preliminary phases (approving and promoting the programme) but also during the implementation phase, as many of these activities request working condition adaptations. Better employee engagement is obtained by involving them from the early steps of the programme.

Therefore, assessment of the risk, screening and workplace intervention programmes to reduce insulin resistance incidence are part of the occupational medicine activity and should be included in the occupational health service provision. Further research to develop tools for on appropriate individual and organizational assessment and strategies for interventions is needed.

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