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The Jiggly-Signal and Wiggly-Receptor Hypothesis: A Novel Perspective towards Pathogenesis and Aetiology of Metabolic Syndrome

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ABSTRACT

The galloping incidence and alarming prevalence of Metabolic Syndrome has put the human life on the edge of a public health catastrophe. Despite the full-blown epidemic and the daily growing list of clinical and biochemical manifestations of the syndrome, not much has been logically addressed with regard to a comprehensive pathogenesis and an integrated aetiology. What, currently, is discussed about metabolic syndrome is exactly the case of examining a huge elephant in the dark. We would like to shed a faint beam of light onto this perplexing issue, and puzzle out the neglected pieces inside the genuine picture of metabolic syndrome and carry the current concept one big step further. We believe that, the present health tsunamy is not merely a metabolic disorder, but also a real chaos at the level of molecular biology and inter-cellular dialogue; a state of metabolo-proteo-genomic disorder presenting itself as a host of metabolic derangements in addition to a generalized cellular dysapoptosis, causing cell senescence, cell swelling, derailed tissue remodeling and eventually a state of chronic oxidative stress. Opposite to dominant concept of over-feeding and related obesity as the initiating factor of metabolic syndrome, we believe that a world-wide ubiquitous environmental insult has led to a state of profound signal-receptor mal-engagement and mis-understanding with a strange pattern of acquired insulin resistance state, emerging explosively in late 1980s. We would like to suggest that, the centripetal obesity, as the stigma of metabolic syndrome, is the result of this newly emerged insulin resistance and the related compensatory hyperinsulinemia, not rather simplistically the cause of insulin resistance syndrome. In effect, one develops metabolic syndrome first, then becomes centrally obese, not the other way round. As a matter of easily understandable fact, in metabolic syndrome, a powerful lipolytic pair-hormone which is GH/IGF-1, is taken over by an obsessed lipogenic substance, that is insulin. Comparable to blowing appearance of metabolic syndrome, we must look for a concurrent, concordant, eruptive and worldwide environmental intruder as the major aetiologic factor, an issue that will be addressed later on.

Keywords

Metabolic Syndrome, Jiggly signal, Pathogenesis, Metabolo-Proteomic syndrome, Wiggly receptor.

Pathogenesis of Metabolic Syndrome

Contrary to stereotyped methods of writing a review article we, by no means, intend to go through all those precious research write-ups and valuable medical literature addressing the Metabolic Syndrome (MbS). This has been carried out professionally very many times, indeed. Thus, the main purpose of this manuscript is to unveil the vital missing parts or neglected aspects and to puzzle out the true location of each piece in the Jigsaw of syndrome X. First of all, we will point out the centrally situated features of MbS to figure out as much as possible about the original picture of this disastrous human health problem. Once, we logically recognized the trues and tricks concerning the above situation, we shall put forward our questions and related suggestions towards the aetiology and core pathogenesis. Here come all those must-to-know informative puzzle pieces, one by one, obviously in purposeful order.

Looking back historically, one would clearly recall the"out-break time-window" for current insulin resistance crisis. Although, there

were scattered reports about hypertensive hypertriglyceridemic, hypertensive hyperuricemic or diabetic dyslipidemic syndromes, but the documentary concerning the rapidly developing constellation of centrally situated obesity, hypertension, dyslipidemia and eventually diabetes was first dramatized in "late 1980s" by an eagle-eyed, genius scientist Reaven GM., and his two distinguished colleagues [1-3]. It is of paramount importance to bear in mind the mentioned date, because it would, later on, become closely linked to a supposable etiologic risk factor.

Of the frightening aspects of MbS is its explosive development over a very short period of time. It was reported as a speculative medical entity (syndrome X) almost thirty years ago, and was suddenly turned into an epidemic, affecting almost 30-50% of world population [4-6]. The critical question that must cross the mind is that; what exactly happened to the world circumstances or to the man- kind life style that was so detrimental and so intrusive to his health in such a short period of time? Was it merely fast food intake, fizzy and sweet drinks like cola or lack of enough physical exercises? Were fast food and sedentary life style really that new, and so odd to human living behavior in early 1980s to completely ruin his health in a blink? The presence of all these putative risk factors in human life had been dating back to many decades or even a century before the banging emergence of metabolic syndrome. We must look for an absolutely odd, eruptive, world-wide environmental intruder to impose such a disruptive impact on human cell biology.

The MbS is not confined to a particular population, ethnic group or a distinct age range; a ubiquitous process that nowhere in the world has remained safe from its deadly invasion. Over the last two decades, it has been stereotypically stated that, over-feeding, fast-food intake, stress and sedentary life style have been the major risk factors for development of metabolic syndrome. The highest prevalence rate of MbS currently belongs to middle-east and south-east Asia, where those risk factor clichés could not be extrapolated to the general population life style at all. Vast majority of people in these areas are strictly bound to the well- known, relatively healthy Mediterranean diet, and fast-food ingestion is not a routine behavior among them.

It has been reported that, overweight and obesity is increasing rapidly and steadily among the US children between 1986 and 1998. By 1998 the prevalence of overweigh children in the US surged to 22%. But, these figures are not merely confined to the well-developed countries. The galloping incidence and tsunamic prevalence of MbS in remote areas of poorly developed countries have become a matter of big challenge indeed. In a pilot survey, carried out by a regional university group in central area of Iran, a population consisted of 6 to 12 year-old elementary school children were investigated. 31% of the children met the Fernandez JR and Dubose Kd's criteria for childhood Metabolic Syndrome. The prevalence of MbS was 19.1% in grade 1 & 2, 25% in grade 3&4, and 36% in grade 5&6. The survey results indicated that the prevalence of MbS was growing up as the children were growing older. The interesting issue about the study was that, they were the inhabitants of a vast deserted territory who would seldom leave their lands unless absolutely necessary. They breed cattle, stroll around the desert for hours every day and usually consume whole-wheat bread, dairy products and a lot of artichoke-like plant. Here comes a straightforward question; what is the operating risk factor for development of MbS in this obsolete, old-fashioned and closed community with absolutely primitive life habits?. The results of this survey was in close agreement with Weiss and Zimmet published data concerning the prevalence of childhood metabolic syndrome [7,8].

Concurrent occurrence and concordant expansion of MbS throughout the world, strongly suggest a globally invasive factor that uniformly affects the human being all around the world, old and young, male and female, black and white. This ubiquitous and pervasive nature of the disorder states in a loud ringing voice that the problem is not merely genetic in origin as well. It is so simple to conceive that inheritable disorders and nasty mutant genes would never penetrate the world-gene pool in just a couple of decades. Comprehensive genetic studies on insulin, insulin receptor and post-receptor signal transduction pathways, would logically argue against a genetic etiology as the sole working risk for MbS [9].

Up to three decades ago, people usually remained thin until fifth decade of their life. They, normally, put some fat pads on the cheeks and around the bellies after their fifties. A rather physiologic process referred to as middle -age spread. But, in contrast to that era, overweight and obesity -particularly centripetal- now begins from pre-school age and rapidly develops into classic MbS before adolescence.

The scientists who work in this research field, are in complete agreement concerning the issue of the insulin resistance as the cornerstone of pathophysiologic process in MbS; that is why the disorder is also referred to as" insulin resistance syndrome". It has also been solidly established that the severity of insulin resistance and the magnitude of compensatory or reciprocal hyperinsulinemia varies widely among suffering individuals [10-12].

Although central obesity is, stereotypically, addressed as the major causative factor for insulin resistance but, it is crystal clear that, the positive correlation between the two parameters has never been strong enough to be taken as the "sole" source of insulin resistance. In one case, we observe an extremely obese subject with rather mild insulin resistance and no overt clinical or biochemical stigmata of MbS, whereas, in the next, an apparently thin individual turns out to be severely insulin resistant and fully symptomatic with regard to known constellation of MbS criteria [13]. Therefore, the common mistake of considering "obesity" as the primary defect or the kick-off point of deviation in metabolism must be critically revised. We would, reasonably, suggest that abdominal adiposity is the "effect" of insulin resistance and ensuing hyperinsulinemia, not the "cause" of it. All subjects with established diagnosis of MbS are more or less obese, but the opposite would not be necessarily true. The obesity of MbS is a particular form of increased total body fat, in which, parallel to the expanded adipose tissues,

the lean body tissues are also increased. The obesity of Mbs is basically different from, namely, hypothalamic obesity in Prader-Willi syndrome or genetic leptin deficiency, in which unleashed fat tissue development is the dominant process compared to lean body mass synthesis. Even in a slightly overweight subject with Mbs, we almost always, come across with a significant insulin resistance and striking hyperinsulinemia, where as in a morbidly obese Prader-Willi syndrome, a mild insulin resistance and negligible hyperinsulinemia is usually expected.

Although, derangements in metabolic profiles like alterations in serum lipoproteins, free fatty acids, blood sugar , uric acid, ApoA1, liver steatosis, non-alcoholic steatohepatitis (NASH), obesity and perhaps hypertension could be taken as the metabolic components of MbS , but what about the ever-growing and endless list of non-metabolic manifestations of MbS, which are, PCOS, BPH, prostate cancer and a wide spectrum of other cancers, immunologic disorders, neurodegenerative diseases, skin tags, finger pebbles, acanthosis nigricans, colon polypes, hyperidrosis, hypertricosis, baldness, acromegaloid facial features, increased serum prolactin , increased serum DHEAS, proinflammatory and procoagulatory states, proteinuria, sodium retention with related edema, muscle cramps, sleep apnea, childhood asthma and so on …..? [12]. It seems, therefore, quite clear that, metabolic syndrome is not merely a metabolic turmoil but also a wide-spread disorder in cell-cell communication and integrated understandable intercellular dialogue. we, though, prefer the term," metabolo-proteomic syndrome" instead of the over-simplified term, that is, Metabolic Syndrome.

More or less the same is the misconception about insulin molecular biology. Since insulin was first discovered for its crucial role in serum glucose modulation, the other biologic aspects of insulin as a powerful growth hormone, a strong mitogenic factor, an apoptosis manipulating signal or a unique anti-lipolytic hormone were easily overlooked.

Insulin, primarily originated in vertebrates as a digestive enzyme. Subsequent to digestion, energy production and enhancement of cell replication and cell discrimination, insulin became adapted to serve as a "growth factor". There is strong evidence that insulin and IGF-II are the primary growth hormones in fetal mammals as well [14-17].

Insulin-like growth factor-1(IGF-1) and proinsulin have a lot in common in terms of their amino-acid structures. As a matter of fact, they are ancestrally linked peptides.

The extremely close resemblance of insulin receptor and IGF-1 receptor is not covered to anybody. Majority of their amino acid sequences are identical, especially on biologically vital domains. Moreover, there is a hybrid IGF-1/insulin receptor variant in which one alpha-beta dimer of insulin receptor is hinged to one alpha-beta dimer of IGF-1 receptor.

The physiopathologic term of “specificity spill-over” was first coined to describe the syndromes in which a hormone exerts its biologic effects through the receptors of another hormone. When two hormones share similar structures and bind nearly identical receptors, they would be able to biologically cross-talk in particular circumstances. It is called "specificity spill-over phenomenon". For example, growth hormone excess in acromegaly could easily interact with prolactin receptors and causes eu-prolactinemic galactorrhea.

In addition to previously known GHRH/GH/IGF-1 secretory cascade, IGF-1 is also produced locally (de novo) in almost all tissues in the body and biologically functions as an autocrine-paracrine growth factor or a vitally important member of cell signal-receptor amplifying system.

Disregarding the cause of insulin resistance, the pancreatic B-cells’ first biologic response to insulin resistance is to increase the serum concentration of insulin with the aim of upgrading the chance of insulin- insulin receptor binding. This results in relative or absolute hyperinsulinemia.

In a setting of insulin resistance, the serum extra insulin (what we call it wandering insulin or orphan signal) tsunamically spills over the IGF-1 receptors all over the body. In this situation, most of IGF-1 receptors would be captured by insulin. This is the consequence of previously mentioned specificity spill - over phenomenon; a full-scale coup- de- etat with announcement of "etat de siege" for GHRH/GH/ IGF-1 regime and a public statement for introduction of newly crowned dictator, the insulin.

Occupation of IGF-1 receptors by insulin, on the one hand and decreased IGFBP-1 production by the liver due to hyperinsulinemia on the other hand, lead to elevated levels of free IGF-1 [18-26]. Increased tissue free IGF-1 blunts pituitary GH release through a direct negative feed-back mechanism. This is the philosophy behind the blunted GH release in dynamic tests of idiopathic growth hormone deficiency (IGHD) in obese individuals. In a study conducted by William et al. it was demonstrated that, insulin resistance in obesity directly blunts the GH response to GHRH. A defect reversed by weight reduction and relative improvement in insulin sensitivity. As a matter of fact, GH secretion, either spontaneous or induced by provocative stimuli is markedly blunted in obese individuals. Obese individuals compared to normal subjects display a reduced half-life, frequency and daily production rate of growth hormone. Blunted GH secretion (GH shortage) in concert with insulin resistance causes a decrease in IGFBP-3 serum concentrations as well. The low levels of IGFBP-1&3 give rise to rapid tissue clearance of free IGF-1. The plasma concentrations of IGFBP3 are regulated by GH. IGFBP3 levels are low in patients with idiopathic growth hormone deficiency (IGHD) and very high in acromegaly. This increase is partially due to a direct effect of GH on IGFBP3 synthesis. The free IGF-1 half -life is as short as 6 minutes, whereas, its bound form has a half-life of close to 16 hours. It is true that IGFBP3 is the most abundant binding protein and has the highest affinity for IGF-1, but IGFBP1 can also bind IGF-1. Hepatic synthesis of IGFBP-1 is under direct control of

insulin concentrations. Increased portal vein insulin levels cause decreased IGFBP 1 gene transcription and though, the IGFBP-1 production. IGFBP-3 abundance in serum is also regulated by a series of special proteases. GH deficient states increase serum levels and potentiate biologic activities of IGFBP proteases. Low levels of serum GH in obesity and insulin resistance, decrease IGFBPs production on the one hand, and upgrade the IGFBPs proteases on the other. The net effect of these various processes is precipitated serum and tissue free IGF-1 clearance. Considering the permissive action of insulin on IGF-1 production in response to GH, patients with severe insulin resistance usually have lower serum IGF-1 values compared to individuals with normal insulin sensitivity [18-26]. Profoundly disrupted human sleep- wake cycle and poor night sleep (chronic sleep debt), as a well-documented cause of significant decrease in 24- hour GH production rate, also contributes to the marked GH shortage in early post-pubertal decades of human life. Thus, the modern day mankind has been seriously deprived from his potent lipolytic pair-hormone (GH/IGF-1) and is practically left defenseless against the lipogenic effects of hyperinsulinemia of insulin resistance syndrome. As a matter of fact, majority of growth hormone and IGF-1 biologic functions are hampered by a wandering gang of insulin. Hence, the biological battle field is almost entirely evacuated from native, stable IGF-1 and the insulin has remained as the sole governor of the metabolo-proteomic bed.

Another key concept in pathogenesis of MbS is the derailment of an amazingly tuned apoptosis modulating system governed by autocrine/paracrine functions of de novo tissue IGF-1. Almost all nucleated cells in the body have the capability of local IGF-1 synthesis and the magic mastery of using IGF-1 as a supervising growth factor to modulate the"metabolomic pathways" and to moderate the "proteomic" processes of cell proliferation, cell discrimination and apoptosis. Hyperinsulinemia results in an insulin rush towards the IGF-1 receptors from top to toes and raises a deep chaotic situation at the metabolomic and proteomic levels. The astounding diversity in manifestations of MbS has roots deep into this horrible salt land. The extremely delicate issue which must be addressed is that, the insulin- whilst capturing the IGF-1 receptor- is predictably unskillful to carry out the entire IGF-1 biologic functions, of utmost significance, the IGF-1 unique lipolytic capabilitie. Therefore, it is absolutely far from expectation that insulin does behave exactly like the native signal. That is why we, facetously call the hyperinsuliemia of insulin resistance syndrome the jack of all trades but the master of none.

A glance at the face of a patient with acromegaly will tell you from A-Z of pure GH/IGF-1 biologic activities, which are, coarse bony facial feature, large fleshy nose, thick lumpy lips and huge multiple nasolabial folds. Those key characteristics demonstrate the immense trophic effects of GH/IGF-1 on bones and soft tissues. Another sine qua non aspect of acromegaly is the marked loss of facial fat or better to say the total body fat, such that the facial skin seems as though tightly sewn to the underneath bony structures. This pathognomonic feature of acromegaly originates from unique lipolytic nature of GH and IGF-1. Exactly opposite to acromegaly stands the idiopathic growth hormone deficiency (IGHD); a short child with an immature face and a characteristic chub and fat gesture. The lack of lipolytic effects of GH / IGF-1 has brought all those thick fat pads about on the cheeks and the belly. Now, let's take a brief look at the face of an individual with type- A insulin resistance syndrome in whom, insulin governs the body instead of IGF-1. At the very first glance, one would obviously figure out that, the facial feature is also coarse and acromegaloid, but to the price of massive facial and body fat accumulation; a true combination of insulin and GF-1 biologic effects. Those thick and extensive fat pads are brought about by inherent lipogenic character of insulin. Even in apparently thin subjects with insulin resistance and MbS, the lean body mass to total body fat ratio is markedly decreased. If we scuba dive further deep into this basic issue, one might say that, in subjects affected by MbS every single cell in the body has become obese from inside. It has been demonstrated that, in insulin resistance state, intracellular fatty acids, long-chain fatty acyl co-A and triacylglycerol are substantially increased compared to lean insulin sensitive individuals. It has also been shown that, treatment with insulin sensitizers (Rosiglitazone) resulted in reduced accumulation of intra cellular fatty acids and their derivatives. In this ominous battle of insulin against IGF-1, the increased total body fat, particularly abdominal adiposity, provokes further resistance to insulin action; a disastrous vicious cycle that desperately whirls and precipitously pulls the helpless and hopeless subject into the massive black-hole of "insulin resistance syndrome". We believe that the metabolic features of MbS are, in fact, the tiny visible tip of a mountainous ice berg. The bottom of this gigantic body is the generalized defect in tissue remodeling due to lack of IGF-1 performance in apoptosis modulation [28,29]. As previously mentioned, the curtailed IGF-1 half-life due to enhanced IGFBP-protease activities and the mingling of wandered insulin to IGF-1 receptors throughout the body, deeply hamper the biologic effects of IGF-1, especially it's extremely important role in cell proliferation and apoptosis. Being in charge, the insulin (as a potent growth factor) is able to fairly manage the cell growth and replication but, when it comes to delicate process of cell refreshment and apoptosis, it is a master of none indeed. The net result of this derangement is marked imbalance between cell proliferation and programmed cell death which culminates in a state of generalized cell senescence and concealed dysplasia with deviation of cell death from clean, non-inflammatory, well-programmed process towards the chaotic, pathologic and pro-inflammatory cell death.

To bring the pathogenesis of MbS to a short and conclusive end, we would suggest that, on a setting of genetic susceptibility and a permissive influence of life style, a strange, surreptitious, ubiquitous and poorly explained acquired insulin resistance has given rise to a reciprocal and compensatory hyperinsulinemia. The magnitude and persistence of this increased serum insulin depends on the inherent biologic soundness of pancreatic B-cells. The surplus of insulin, widely and wildly, spills over the IGF-1 receptors almost everywhere in the body that brings about a chaotic situation in which, the aberrant signal-receptor pathway leads to a profound derangement in lioplytic/lipogenic equilibrium and

also a disastrous deviation in proteomic processes. Thus, the net effect of this aberrancy is a hodgepodge of insulin /IGF-1 biologic activities ending up with metabolo-proteomic syndrome.

A logical hint towards aetiology of metabolic syndrome

When we address the binding process of peptide hormones like insulin and their cell-surface filamentous receptors, we are talking about extremely small, angstromic structures with awesome delicacy and astounding complexity. The binding facets of insulin and insulin receptor are even of sub-angstromic dimensions. There are two binding facets on each delicately conformed insulin peptide. For optimum and economic insulin/insulin receptor binding, each facet of insulin must exactly come across to one of the two insulin receptors' alpha subunit binding sites, so that, one insulin molecule lodges right between the two alpha subunits of insulin receptor; a molecular biologic phenomenon which is thousands of times more stringent and more brittle than the embarkation of space shuttle on international space station. Even a trivial and hardly noticeable shock wave or a weak electromagnetic field or a parasitic electromagnetic (EM) wave might interfere with and disturb the intimacy, privacy and binding affinity of signal/receptor engagement. Even an angstromic skew between insulin binding facets and insulin receptor binding sites would result in crucial deviation in signal transduction and resistance to insulin action. Now let's briefly review the most influential changes in human life style between1980-1995, the time- window of MbS outbreak. What might have happened to human environment to affect the human physiology so dramatic and so profound close to that particular era? It is quite feasible to recall that, none of the routinely claimed and simply blamed risk factors for metabolic syndrome, namely; over-feeding, fast-food access, emotional stress, sleep debt or physical inactivity were utterly new to the mankind at that time. Were fast food and sedentary life style really that new, and so odd to human living behavior in 1980s to completely ruin his health in a blink? The presence of all these putative risk factors had been dating back to many decades or even a century before the banging emergence of metabolic syndrome. We must look for an absolutely odd, explosive, and world-wide environmental intruder being able to impose such a dramatic impact on human cell biology. The most striking and visibly impressive life style change in 1980s was the technologic break-through of cell-phone communication. The first hand-held cell phone was demonstrated by John Mitchell of Motorola in 1973, and by 1983 the mobile phones were launched to the market and became commercially available by M. Cooper. From 1990 to 2011, worldwide cell-phone subscribers grew from 12.4 million to over 6 billion, penetrating above 90% of the global population, an innovative invention that gave way to another by-product applying more voluminous and much energetic EM microwave that is EM. Micro-waves used for internet data transfer through mobile phones; a full-scale "big bang" of electromagnetic microwave irradiation of the whole world. EM waves created by the vibration of an electric charge have both an electric and a magnetic component. We know that light acts like a wave, but at the same time it acts like a particle as well. The particle phase of light is called photon. Low-energy photons like radio-frequency wave photons tend to behave more like waves, while higher energy photons like microwaves behave more like energy-carrying particles called quantum. EM photons travel with a speed of (c) in vacuum, whereas, through material medium, they propagate with net speed of less than (c) creating a state of non-resonant vibration in sub-structural particulates of the medium by energy absorption and re-emission. Different materials cause different amount of delay in EM wave transmission, depending on the distance between their atoms, the lesser the distance the lower the speed of EM wave propagation [30]. Thus, it clearly implies that the particulate phase of EM wave, that is the photon or quantum, collides with particulates of solid mediums, for example, insulin molecule and its out-stretched, free-floating cell-surface receptor. It is though, logically perceivable to suggest that, the shocking, shaking and vibrating effects of passing EM microwave quanta might trivially jiggle the signal and insensibly wiggle the receptor. We already know that the microwaves emitted by mobile phones are able to increase the tissue temperature, especially the looser ones like brain. So, it is reasonable to assume the issue of repeated bumping and friction between EM wave energy-carrying quanta and human tissues. One might argue that the amount of energy delivered by a single quantum is too little to meaningfully displace a macromolecule like insulin receptor. The logical answer is that, we are facing with more than seven billion sources of EM wave emission, firing concurrently and sometimes synchronous towards us; an all-out big bang of eradicating EM microwave irradiation of the earth.

We believe that in particular circumstances like hyper-synchronic bombardment of a biologic signal or free-floating receptor by EM microwaves, the created shocks and shakes might gain proper magnitude and enough strength to impede the signal- receptor alignment of binding process, causing insulin resistance. We would also suggest that, the revolving magnetic fields of electromagnetic waves might affect the poorly understood, probably electro-chemical process of insulin /insulin receptor affinity as well.

With respect to different vulnerability towards metabolic syndrome, we would suggest that, the presence of various non-sense mutations on the path of insulin, insulin receptor and post receptor signal cascades, in addition to permissive effects of over-feeding, lack of exercise and chronic sleep debt give rise to different levels of susceptibility for development of metabolic syndrome. Most of current research works concerning microwave health hazards are concentrated or better to say distracted towards brain glucose metabolism and ensuing tissue heating in cell phone users. There are also studies addressing the increased incidence of brain tumors and the possible derangement in cell apoptosis linking the subject to autoimmune disorders. In a study conducted by Kerman M., it has been clearly demonstrated that microwave irradiation at mobile phone frequency levels causes a marked oxidative stress in hypocampus neurons [31]. Pro-inflammatory serum biomarkers (IL-6 and TNF-α) were also significantly increased in microwave irradiated Fischer rats [32-33]. We would like to hypothesize that chronologically parallel to the EM microwaves big bang, the metabolic syndrome was first reported in 1988 in Banting lecture, and then concordant to the number of cell-phone subscriptions,

expanded from a few speculative cases (syndrome x) to a terrifying world-wide epidemic, afflicting billions of people all around the globe. It seems rather strange that we conduct numerous time-consuming longitudinal cohort or case-control studies to find the relationship between, for example, colon cancer and amount of consumed dietary fiber, but we do not simply plot the relationship between the number of cell phones sold yearly and the incidence and prevalence of metabolic syndrome from 1990 onwards.

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