

A Novel Look Into Pathogenesis and a Logical Hint towards the Etiology of Metabolic Syndrome: The Jiggly-Signal and Wiggly-Receptor Hypothesis!

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Abstract

The galloping incidence and the alarming prevalence of Metabolic Syndrome (MbS) has put the human life on the edge of a certain catastrophe. Despite the full-blown epidemic presentation and ongoing and ever-expanding list of clinical and biochemical manifestations of the syndrome, not much have been logically addressed with regard to a comprehensive pathogenesis and an integrated etiology. What we have so far heard about MbS is more or less like the old Indian tale of examining a huge elephant in the dark. We would like to open a small but sun-view window and shed a faint beam of light onto this perplexing issue, and puzzle out the neglected pieces of a semiset picture and carry the current concepts regarding MbS one big step further. It is crystal clear that, metabolic syndrome is not merely a metabolic disorder, but also a real chaos at the level of molecular biology and inter-cellular dialogue; a state of generalized cell swelling, cell refreshing defect, cell senescence, chronic oxidative stress, and derailed tissue remodeling due to diverse unusual tissue growth factor expressions.

Opposite to common belief of over-feeding and obesity as the initiating factor of metabolic syndrome, we suggest that a world-wide ubiquitous environmental insult has led to a state of profound signal-receptor mal-engagement and misunderstanding; an all-out syndrome which is unequivocally tied up to a strange and totally new pattern of insulin resistance state being emerged out of real blue in late 1980s. What we are trying to propose is that, the centripetal obesity of metabolic syndrome is the result of a recently broken out overwhelming insulin resistance state and its reciprocal, compensatory hyperinsulinemia, not simply and solely the cause of it. We would like to argue that in metabolic syndrome the insulin resistance comes first and leads to central adiposity. At the end, an all-embracing environmental risk factor will be logically hinted at as a novel etiologic clue.

Keywords: Metabolic Syndrome, Pathogenesis, Jiggly Signal, 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 of the issue, and to puzzle out the true location of each piece in the Jigsaw of syndrome X. First of all, we 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 relevant suggestions towards the etiology and core pathogenesis. Here come all those must-to-know informative puzzle pieces, one by one, in purposeful order from 1 to 20.

Looking back historically, one would clearly recall the outbreak time-window of 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 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 presumptive etiologic risk factor.

Of frightening aspects of MbS is its explosive development over a very short period of time; a mysterious feature that might directly refer to the dominant etiologic risk factor. MbS was reported as a speculative medical entity almost twenty five years ago and suddenly turned into a worldwide health problem affecting more than 30-50% of world population so far [4-6]. The first and perhaps the most critical question that crosses the mind is that; what exactly

happened to the world circumstances or to the man-kind life style which was so detrimental to his health in such a short period of time?. Was it simply fast food intake, sedentary life or stress? Utterly they were not. Because what repeatedly and stereotypically expressed as major risk for rapidly developing insulin resistance state had never been new to human life in 1980s. We must search for a banging environmental insult overwhelming the whole world in a short course of time, say, a decade or two; a striking phenomenon with disruptive impact on human cell molecular biology namely, insulin/insulin receptor binding difficulties resulting to an acquired pattern of worldwide insulin resistance.

The MbS is not confined to a particular population, ethnic group or a distinct age range; a ubiquitous, pervasive process that nowhere in the world has remained safe from its deadly invasion. It is quite surprising to hear that the highest prevalence rate of MbS currently belongs to middle-east and south-east Asia, where the commonly proposed risk factors are, by no means, a matter of extrapolation towards general population life style. Vast majority of people in these areas are strictly bound to a well-known healthy eating habit called Mediterranean diet.

The development of overweight and obesity has rapidly and steadily increased among the US children between 1986 and 1998. By 1998 the prevalence of overweight children in the US surged to 22%. But, these figures are not merely confined to the developed countries. The galloping incidence and surging prevalence of MbS in remote areas of developing countries have become a matter of big challenge indeed. In a pilot survey, carried out by a university group in central area of Iran, 6 to 12 years old elementary school children were investigated. Thirty-one percent 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 of elementary schools. The results of the survey indicated that the prevalence of MbS was soaring as the children were growing older. The amazing issue about the study was that they were the inhabitants of a vast deserted area (kavir-e-loot) who would seldom leave their territory 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 an artichoke-like desert 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 primitive life habits? This survey is clearly, in close agreement with Weiss and Zimmet published data [7,8].

Concurrent occurrence and concordant expansion of MbS throughout the world, strongly suggest a globally invasive risk factor that uniformly affects the human being all around the world, east and west, rich and poor, male and female, old and young and black and white. This characteristic feature of the disorder states in a loud ringing voice that the problem is not merely genetic in origin indeed. 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 pure genetic etiology as the sole working risk factor for MbS [9].

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

The scientists working on this field are in complete agreement concerning the issue of 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 hyperinsulinemia, vary widely among suffering individuals [10-12].

Although central obesity has, stereotypically, been addressed as the major causative factor for insulin resistance but, it is crystal clear that, this positive correlation has never been strong enough to be considered as the "sole" influencing source of insulin resistance. In one case, we observe an extremely obese subject with rather mild insulin resistance with no overt clinical or biochemical stigmata of MbS, whilst in the next case, an apparently thin individual, turns out to be severely insulin resistant and fully symptomatic in terms of MbS [13]. Therefore, the common misconception of considering "obesity" as the basic defect and the kick-off point of deviation in metabolism must be critically revised. We would suggest that, abdominal adiposity is the "effect" of insulin resistance and ensuing hyperinsulinemia, not the "cause" of it. All subjects with firmly established diagnosis of MbS are more or less obese, but the opposite is not necessarily the case. The obesity of MbS is a particular form of increased total body fat, in which, parallel to the expanded adipose tissues, the lean body mass is also increased. The obesity of MbS is basically different from, namely, hypothalamic obesity in Praderwilli 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, whereas in a morbidly obese Prader-willi syndrome, a mild insulin resistance with a negligible hyperinsulinemia is expected.

Although, derangement in metabolic profiles like alterations in serum lipoproteins, free fatty acids, blood sugar, ApoA1, ApoB100, non-alcoholic liver steatosis, non-alcoholic steatohepatitis (NASH), obesity and perhaps hypertension could be considered as the metabolic components of MbS, but what about the ever-growing, endless list of non-metabolic manifestations of MbS, i.e. PCOS, BPH, prostate cancer, skin tags, finger pebbles, acanthosis nigricans, colon polypes, hyperidrosis, hypertrichosis, baldness, acromegaloid facial features, hyperuricemia, increased serum prolactin, increased serum DHEAS, decreased SHBG, increased IGFBP proteases, increased prostate specific protease PSA,

proinflammatory and procoagulatory states, proteinuria, sodium retention and related edema, muscle cramps, sleep apnea, childhood asthma and so on? [12]. It sounds, therefore, totally clear that, metabolic syndrome is not, merely, a metabolic turmoil but also a widespread, head-to-toe disorder in cell-cell communication and integrated understandable intercellular dialogue. We, though, prefer the rational term of metabolo-proteomic syndrome instead of an over-simplified label that is metabolic syndrome.

More or less the same is the misunderstood issue regarding the insulin molecular biology. Since insulin was first discovered for its crucial role in serum glucose modulation, the other basic biologic aspects of insulin as a powerful growth hormone, a strong mitogenic factor, an impressive 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].

The structures of insulin-like growth factor-1 (IGF-1) and proinsulin have a lot in common. As a matter of fact, they are ancestrally linked peptides. The extremely close resemblance of insulin and IGF-1 receptors is not covered to the scientists at all. 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 α - β dimer of insulin receptor is hinged to one α - β dimer of IGF-1 receptor.

The pathophysiologic term of specificity spill-over was first coined to describe the syndromes in which a hormone exerts its effects through the receptors of another hormone. When two hormones share similar structures and bind nearly identical receptors, they could 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 euprolactinemic galactorrhea.

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

Disregarding the cause of insulin resistance, pancreatic β -cells' first biologic response to insulin resistance is increased 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, and in the presence of IGF-1 shortage, 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 are being captured by insulin. This is the result of previously mentioned specificity spill over phenomenon; a full-scale coup De et a. an announcement for state of siege for GHRH/GH/ IGF-1 regime and a statement concerning the 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, lead to elevated levels of unbound IGF-1. Increased tissue unbound 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 which was reversed by weight reduction and relative improvement in insulin sensitivity. Obese individuals compared to normal subjects display a reduced half-life, frequency of secretory episodes 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 results in rapid tissue clearance of free IGF-1 (IGF-1 shortage). 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 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. Although the IGFBP3 is the most abundant binding protein and highest affinity for IGF-1, the IGFBP1 can also bind IGF-1 to a lesser extent. It is noteworthy that hepatic synthesis of IGFBP-1 is also 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 biologic activities of IGFBP proteases. Reduced serum levels of GH in obesity and insulin resistance, decreases IGFBP production on the one hand, and upgrades the IGFBP proteases on the other. The net effect of these two various processes is enhanced serum and tissue free IGF-1clearance. Considering the permissive action of insulin on IGF-1 production in response to GH, patients with severe insulin resistance have lower serum IGF-1 values compared to individuals with normal insulin sensitivity [18-26].

Thus, the modern day mankind is being seriously deprived from his youth fountain, that is, GH and free IGF-1 and being desperately left defenseless against the disruptive effects of hyperinsulinemia of insulin resistance syndrome. As a matter of fact, the highly delicate biologic functions of GH and IGF1 are opposed by a riotous gang of insulin. In a dramatic presentation, one might almost say that the whole biological battle field is entirely evacuated from highly educated native inhabitant insulin like growth factors while insulin is being remained as the sole ruler of the metabolic bed. A

powerful lipolytic factor is dethroned, while an obsessed lipogenic substance is let unleashed out. With this explanation one would figure out why the human being has become prone to obesity.

Another key concept in pathogenesis of MbS is the derailment of an amazingly tuned cell apoptosis modulating system governed by autocrine-paracrine function of the de novo tissue IGFs. Almost all nucleated cells in the body have the mastery of local IGF-1 synthesis and the magic capability 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 rampage on IGF-1 receptors from top to toes causing a deep chaotic situation at the metabolomic and proteomic levels. The astounding diversity in MbS’ manifestations has root deep into this boundless marshland. In effect, insulin, as a nonspecific signal, does not normally bind or interact with IGF-1 receptor, but, illegitimately intermingles with it. Therefore, it is far from expectation that insulin does behave exactly like the native signal. That is why we, facetiously name the hyperinsulinemia of insulin resistance syndrome a jack of all trades but the master of none.

Even a quick glance at the face of an acromegalic patient will tell us from A-Z of pure GH/IGF-1 biologic activities, which are, coarse bony facial feature, large fleshy nose, thick lumpy lips and multiple overlapping nasolabial folds. These clinical stigmata clearly demonstrate the immense trophic effects of GH/IGF-1 on bones and soft tissues. The next and ever-existing feature of acromegaly is the absolute lack of facial fat, such that the facial skin seems like tightly sewn to the underneath bony structures. This pathognomonic or better to say, the sine qua non 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 chubby gesture. The absence of lipolytic effects of GH and IGF-1 has brought about all those thick fat pads on the cheeks and the belly. Now, let’s take a closer look at the face of an individual with type A of insulin resistance in whom, the insulin excess 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 abdominal fat accumulation; a true amalgam of insulin and IGF-1 biologic effects.

If we Scuba dive further deep into this basic issue, we would observe that, in insulin resistance syndrome 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 subjects. It has also been shown that, treatment with insulin sensitizers (Rosiglitazone) results in reduced accumulation of intra cellular fatty acids and their derivatives. Albeit, in the 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 whirls and pulls the helpless and hopeless subject inside the massive black-hole of

“insulin resistance syndrome”. We, beyond any doubt, believe that the metabolic features of MbS are, in fact, the tiny visible tip of a mountainous ice berg, and the bottom of this gigantic body is a generalized defect in tissue remodeling due to overwhelmed IGF-1 performance in apoptosis modulation [28,29]. As previously mentioned, the curtailed IGF-1 half-life due to enhanced IGFBP-protease activities and over spillage of wandering insulin onto IGF-1 receptors throughout the body, dramatically dampens the biologic effects of IGF-1, specially, it’s extremely important role in cell proliferation, cell discrimination and cell apoptosis. Being in charge, the insulin (as a potent growth factor) is also able to fairly manage the cell growth and replication but, when it comes to delicate cell refreshing and apoptosis regulating processes, it functions pretty clumsy indeed. The net result of this derangement is marked imbalance between cell proliferation and programmed cell death; a state of generalized cell senescence, oxidative stress and concealed cellular dysplasia; a state of deviant cell death from clean, non-inflammatory, programmed phenomenon towards the chaotic, pathologic inflammatory cell death. Now we might have a better understanding of the operating mechanisms behind the proinflammatory state, raised CRP, disturbed tissue remodeling in BPH, prostate cancer, PCOS, colon polyp formation, and so on in metabolic syndrome.

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, compensatory hyperinsulinemia. The magnitude and persistence of this hyperinsulinemia depends on the inherent biologic soundness of the peoples pancreatic β -cells. This is the philosophy behind the diversity of clinical and biochemical manifestations of patients affected by metabolic syndrome.

Putative Etiology of Metabolic Syndrome

While addressing the peptide hormones and cell surface filamentous receptors, we are talking about extremely small, angstromic structures with awesome delicacy and astounding complexity. The binding facets of insulin molecule are of even 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 two insulin receptors’ - subunit binding sites, in such a way that one insulin molecule becomes enlaged right between the two -subunits of insulin receptor; a molecular biology phenomenon which is thousand times more stringent and more interruptable than the space shuttle anchoring on International Space Station. Even a slight skew or an angstromic mal-alignment between insulin binding facets and insulin receptor binding sites would result in substantial deviation in signal transduction and resistance to insulin action. Even a trivial and hardly noticeable blowing, blasting or fluttering effect or a weak electromagnetic field induced by repetitive electromagnetic (EM) waves might interfere with and disturb the intimacy, privacy or biologically speaking the affinity of signal/receptor engagement. Now, let’s look back and review all those dramatic changes in human life mentioned

earlier in this manuscript over the 1980s, the MbS outbreak time-window. What exactly happened to the human life that was so detrimental towards the man kind health in just a few decades? None of the usually claimed and simply blamed risk factors for metabolic syndrome were new to the mankind at the time of MbS out-break, namely; overfeeding, fast-food access, macronutrient ingestion, sleep dept, emotional stress or physical inactivity. Over the years between 1980 and 1990, the most striking change in human environment which was unique, unprecedented and out-of-the-ordinary 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 they were launched and became commercially available to public in 1983. From 1990 to 2011, worldwide cell phone subscription 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 tremendously energetic EM microwaves, that is internet data transfer through mobile phones, the mobile networks; a full-scale “big bang” of electromagnetic microwave irradiation of the whole world. It is totally perplexing why such a dramatic catch up in cell phone subscriptions and strange mass hysteria regarding mobile phone abuse with incredible environmental irradiative pollution are not being noticeably considered as a putative risk to human molecular biology. Of few ongoing research projects, mainly are concentrated on brain glucose metabolism and ensuing tissue heating in cell phone users. Some studies have addressed the increased incidence of brain tumors and the possible derangement in cell apoptosis linking the subject to autoimmune disorders. In a study conducted by kanu M et al. it was clearly observed that microwave radiation at mobile phone frequency levels caused a marked oxidative stress in hippocampus neurons. The same results were also supported by Sokolovic and Moussa. Pro-inflammatory serum biomarkers (IL-6 and TNF- α) were also significantly increased in microwave irradiated Fischer rats [30-32]. These preliminary studies, though limited in number, must warn the scientists to get involved and do not let the issue kept deliberately neglected.

We are trying to biologically hypothesize a surreptitious derailment in human molecular biology mediated by tremendous, potentially disastrous EM microwave irradiation of the earth. Chronologically concordant to the EM wave big bang, the early cases of metabolic syndrome were first reported in 1988, and exponentially expanded from a few speculative cases to a terrifying world-wide epidemic, afflicting billions of people all over the globe. Why do we deny such a straightforward correlation? I mean the contemporaneous appearance and concordant expansion of the world-wide microwave big bang and the surging prevalence of metabolic syndrome? It is actually strange that we conduct numerous longitudinal cohort or case- control studies to find, for example, the cause-and-effect relationship between colon cancer and dietary fiber, or frequency of ejaculation and the incidence of prostate cancer, but we do not simply plot the number of cell phones sold yearly and the incidence of metabolic syndrome from 1990 onwards. If it is done, one would clearly observe the absolute positive correlation between

the above variables with a non-oscillating “r” close to +1. In effect, we would suggest that, the overwhelming electromagnetic fields might disturb the signal-receptor binding affinity and the blowing and fluttering effect of EM microwaves might negatively affect the alignment of signal/receptor binding facets. As a matter of fact, in response to hardly detectable blasting influence of ever-blowing EM microwaves, the insulin molecule could constantly jiggles and the out-stretched, filamentous cell-surface receptor might repeatedly wiggles in such a way that the signal-receptor affinity becomes disturbed and the proper signal-receptor interaction and perceptible signal transduction gets interfered, culminating in a state of Jiggly-signal and wiggly-receptor, insulin resistance and metabolic syndrome.

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