In a recent report, the world health organization (WHO) sees a global epidemic of chronic diseases in the offing. Absent an infectious pandemic like the avian flu virus presently incubating in Southeast Asia, chronic diseases portend to be the biggest health care concern the world over in the near future. Chronic diseases are already a major health care concern in technologically advanced countries. According to the WHO, that will increasingly be reflected in the epidemiological data.

It is for good reason, then, that ever-greater emphasis is placed on understanding those mechanisms that contribute to the onset of chronic diseases. Lately, inflammatory response has been touted as the mechanism implicated in a wide swath of chronic conditions. While it makes sense on face value, it is not yet entirely clear whether inflammation might be the root cause, or a result of, some other precipitating mechanism(s). Inflammation does aggravate the symptoms of a number of diseases, though, and as such, it may complicate the natural progression of a given condition. For instance, pro-inflammatory cytokines are presented in diverse conditions such as arthritis, cancer, and diabetes. Further, they are found equally in obese individuals and individuals in a state of stress. Which bespeaks that a primary role for inflammation per se in the onset of chronic diseases is rather questionable. Therefore, it is quite plausible that a bio-molecule—a protein, a metabolite, toxin, or hormone—could well be the common denominator in the onset of chronic, age-related diseases.

First off, the question forces itself as to why is it necessary to presume a common substance or pathway in chronic diseases. A cursory look at the clinical presentation of some of the more pervasive diseases, and mechanistic overlaps among them, suggests that a few metabolic pathways would likely be shown to at least initiate the processes that ultimately manifest themselves as heart disease, diabetes, obesity, neurodegeneration, or cancer.

What could such pathways be? For certain, the pathways would likely differ from condition to condition. It is quite reasonable to posit, however, that clusters of unrelated diseases may have a finite number of bio-agents that triggers (a) disease process(es) with disparate physiologic networks leading to various disease states. For the purposes of this discussion, the cluster of obesity-diabetes-heart disease, and its ramifications, is considered.

Why? It is because there is an alarming upsurge in the incidence of obesity and diabetes worldwide. In fact, in the United States, roughly two-thirds of the population is either overweight or morbidly obese. Obesity can cause considerable problems, if accompanied by high blood pressure and abnormalities in glucose and lipid (body fats) metabolism. These apparently divergent dots are connected together by what is referred to as insulin resistance, a reduced sensitivity in the body to the action of insulin.

To better appreciate this phenomenon, it is best to recapitulate the main function of insulin, which is to transport sugar from the blood into muscle and fat cells where it is “burnt” to produce energy. On occasion, however, this transport service fails. This is called insulin resistance or, alternately, reduced insulin sensitivity. To overcome insulin resistance, the pancreas, which produces insulin, churns it out in larger amounts. If insulin is not produced in sufficient amounts, blood sugar levels are increased, which may cause Type II diabetes. More often than not, however, the pancreas does produce insulin to normalize blood sugar levels. There is a price to pay, though. In addition to being a chariot for glucose to be transported to target cells, insulin is also a powerful hormone. Thus, excess insulin may signal the kidney to retain salt. Increased renal retention of salt means greater likelihood of hypertension in the affected individual. This is but one example as to how far the insulin problem—excess or deficiency—may transcend.

Generally speaking, how would insulin excess contribute etiologically to other conditions? Starting with the well-known effects of diabetes on the heart, increased amounts of insulin damage the lining of arteries. As a result, triglycerides and low-density cholesterol (LDL) levels are elevated, which leads to the clumping of blood cells, making them more prone to form clots and constrict blood vessels. It is axiomatic, then, that insulin resistance gives rise to the tria of diabetes, heart disease, and high blood pressure, which alone can sufficiently damage the heart and kidneys. Simply, if left unchecked, insulin resistance may cause heart attacks and strokes. In fact, a recent study reported that high insulin levels—in, of, and by themselves—are powerful predictors of heart attacks, especially among younger men.

Thus, men with high insulin levels had upward of a three-fold risk of heart attack.

As a result, greater emphasis is now being given to improving the understanding of insulin’s role in clustering of cardiovascular risk factors. The expectation is that this approach will facilitate newer treatments. This is already the case for stroke, as a new treatment is being tested presently at the National Institutes of Health (NIH).

As noted above, insulin is more than a carrier for sugar. It can direct aberrant cells to grow more robustly and become cancerous. This is because cancer cells have between six to ten times the number of insulin receptors compared to their normal counterparts. Insulin receptors are proteins that latch onto this hormone. Consequently, upon reaching a collection of preexisting cancerous cells, excess insulin triggers its unbridled growth. Hence, to a transformed cell insulin provides the food and energy source for growth.

Interestingly, several different types of cancers are particularly responsive to insulin—especially those of colon, breast, endometrial, pancreatic, and prostate. Insulin may be particularly pernicious in cases of hormone-dependent cancers. In such cases, one hormone (insulin) reinforces another (estro-
The Collateral Damage

...gen, for example, in breast cancer), and makes the growth even more ferocious. It is nary surprising then that breast cancer cells may have a specialized version of insulin receptor (fetal insulin receptor) which can make tumor growth and cancer progression far more robust.4

The productive interaction among hormones is most easily noted in polycystic ovary syndrome, which affects one in ten women in the United States, and is the leading cause of infertility. High levels of insulin trigger the production of excess androgens in the ovaries. Androgens disrupt the regular growth of the ova and induce menstrual cycles to prevent pregnancy. What is more, these androgens can also cause male-pattern hair growth on the face and other unpleasant changes in the appearance. It is for good reason, therefore, that the polycystic ovary syndrome is now increasingly managed by insulin sensitization. Needless to say, treatment of insulin resistance is relevant beyond fertility issues, since untreated women with this syndrome have more than seven times the risk of heart disease and three times the risk of diabetes.

Lately, solid evidence seems to support the notion that diabetes and heart disease may be partially responsible for neurodegeneration. The basis for that, too, can be attributed to large amounts of insulin in the blood. As such, insulin resistance ensured that less insulin is available in the brain. Why does the brain need insulin? It is known that cells in the brain’s memory center have an abundant supply of insulin receptors. A spike in insulin improves memory and performance. Hence, if there is no insulin, brain function begins to decline. It has already been pointed out above that insulin has corrosive effects on blood vessel linings. Excess insulin in the bloodstream literally chokes the portals in the blood vessels through which insulin transfers sugar into the cell. If this persists, the brain cells will be starved of the energy they need to function at par. If starvation is prolonged, it could set the stage for some cases of Alzheimer’s disease, Parkinsonism, and Huntington’s disease. Notably, tentative evidence implicates insulin in the removal of β-amyloid, a hallmark of Alzheimer’s disease.5

Numerous models have been propounded to explain what Alzheimer’s disease is and how it may present itself. Among those, insulin is but one, and a Johnny-come-lately, too. Irrespective of which etiological factor(s) by what precise mechanisms(s) to full-blown Alzheimer’s diseases, its symptoms have been reported to improve upon replenishing insulin to the patients’ brains. It is not known just yet how long the improvement would last, let alone whether insulin therapy might even help reverse neurodegeneration. Parenthetically, neurodegeneration is likely to be one of the most telling signs of the ever-aging population throughout the world, and an urgent health care challenge among the ensemble of chronic diseases.

The foregoing summarizes a mere handful of chronic diseases in which insulin resistance may be implicated. Both the excess and deficit of insulin define a panoply of chronic conditions. Simplicistically, the basic mechanism of disease can be classified in a handful of categories, including genetic predisposition, pathogenic organisms (such as, viruses, bacteria, fungi, etc.) inflammation, and degeneration. As noted above, insulin resistance can accelerate degenerative processes, which under otherwise normal conditions would be a consequence of cellular senescence and/or aging.6 Equally, insulin resistance can further intensify the inflammatory response, which could potentially be tamed and resolved were it not for budding obesity and cellular stress that increased weight engenders.

Interestingly, however, insulin resistance can be managed by relatively simple approaches, and, genetic predisposition notwithstanding, its major brunt can be at least forestalled. In fact, it could be argued that in some cases, insulin resistance may be the most readily amenable to such simple changes and, therefore, it may reduce the collateral damage in its wake significantly. For instance, it is known that lifestyle modification can significantly alter the risk profile of the cluster of heart disease, diabetes, and high blood pressure.

It must be emphasized, however, that the role of insulin in the onset of chronic diseases is still a work in progress. Whether it will be ultimately shown to be central to lifestyle-related conditions awaits additional research and insights it is likely to yield. The preponderance of evidence to date does point out that even if insulin resistance were to be relegated to a secondary or even tertiary role in pathogenesis, its timely management could potentially avert more serious manifestation of chronic diseases.

Selected References

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