

• **Commentary**

# Time to change from a simple linear model to a complex systems model

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A simple linear model to test the hypothesis based on one-on-one relationship has been used to find the causative factors of diseases. However, we now know that not just one, but many factors from different systems such as chemical exposure, genes, epigenetic changes, and proteins are involved in the pathogenesis of chronic diseases such as diabetes mellitus. So, with availability of modern technologies to understand the intricate nature of relations among complex systems, we need to move forward to the future by taking complex systems model.

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We used to hypothesize that a particular exposure is responsible for a certain health outcome. Actually, this hypothesis was from observation that a bacterial agent caused an infectious disease back in the 19th century. Robert Koch was the key champion for this hypothesis. He postulated that the microorganism must be isolated from a diseased patient and grown in pure culture and the cultured microorganism should cause the same infectious disease when introduced into a healthy person. He added to the postulates that the microorganism must be isolated again from the diseased host and identified as being identical to the original specific causative agent. However, viral diseases and some bacterial diseases did not follow Koch's postulates. Even at the time of Robert Koch, many scientists believed that Koch's postulate was sufficient but did not necessarily establish causation.

However, the assumption that one causative agent causes one corresponding disease has dominated in the scientific community since the 19th century. Most life science researchers have tried to evaluate the relationship between a causal factor and a clinical outcome and to further investigate the mechanism underlying the one-on-one relationship. Now, we have astonishingly flourishing reports on the relationship and mechanism between a causal factor and a clinical outcome. For instance, there have been incredibly numerous reports on the relation between physical activity and diabetes mellitus, all showing that reduced

physical activity is responsible for development of diabetes mellitus. Based on this solid evidence, physicians recommend an increase in physical activity to prevent diabetes mellitus and promote better health.

On the other hand, we can easily find another report which shows that stress is related to diabetes mellitus and recommends reducing stress levels to prevent the disease. We see many reports on diet and obesity as well. Recently, many studies on the relation between exposure to chemicals, such as dioxins and phthalates, and diabetes mellitus are asking us to extend risk factors. Therefore, in the case of diabetes, there must be more than one causative agent responsible for the development of the disease.

So, how can we apply a simple linear relationship for the evaluation and management of diseases like diabetes mellitus? Researchers now use multivariable models based on linear or even non-linear relations to complement the shortcomings of simple linear relationships. However, even with multivariable models, they still try to test the hypothesis that a certain risk factor causes diabetes mellitus considering or controlling other factors.

Now, we understand that nutritional intake, glucose metabolism, insulin production and action, mitochondrial role, genetic constitution, and epigenetic regulation are closely involved in the development of diabetes mellitus. Not only these bodily mechanisms, but psychological stress and environmental expo-

sure are also known to play important roles. We now come to know that not just one, but many, factors are involved in the pathogenesis of diabetes mellitus. In fact, the involved factors are components of different systems such as chemical exposure, genes, epigenetic changes, and proteins. We may call such systems exposome, genome, epigenome, or proteome [1].

Fortunately, we have modern technologies with the ability to understand systems, not just components. The technologies are essential to enable us to grasp the complex idea of how different systems work together. Now, understanding the role of complex systems in the pathogenesis or progression of diseases requires a new perspective on how that complexity works in relation to diseases. Basically, structure and function as well as stimulation and response are entangled in the complex systems network. Very importantly, this network is constantly changing according to life stage. For instance, complex systems work differently depending on age, namely from fetus to the elderly.

In the 21st century, we now have advanced technologies of information, analysis, and recognition, and have the capability to understand the complex systems in and around us [2]. So, this

is the time to depart from the obsolete idea of simple relations based on one-on-one correspondence to a complex systems model based on a complex network for really understanding diseases.

## Conflict of Interest

The author has no conflicts of interest associated with material presented in this paper.

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