

# Protein Aggregation: A New Challenge in Type-II Diabetes

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## Abstract

Accumulation of misfolded proteins or their aggregates in various organs is the hallmark of protein misfolding disorders (PMD), including Alzheimer's and Parkinson's Diseases. Recent studies have shown accumulation of protein aggregates in some non-neurodegenerative diseases like cancer and type-II diabetes. Deposition of toxic aggregates of islet amyloid polypeptide (IAPP) or amylin may cause dysfunctioning and loss of  $\beta$ -cells leading to impaired insulin release and cause type-II diabetes. In this review, we will discuss the aggregation of islet amyloid polypeptide (IAPP) or amylin and associated toxicity in pancreas promoting type-II diabetes.

**Keywords:** Protein aggregation; Islet amyloid polypeptide (IAPP) or Amylin; Type-II diabetes

## Introduction

From many decades, researchers have been aware of the formation of insoluble protein aggregates in many neurodegenerative diseases such as Parkinson's, Alzheimer's and Huntington's diseases [1] but there are some reports which showed the presence of insoluble amyloid deposits in diabetes mellitus type 2. Diabetes is a very common but a serious chronic disease in which either body can't produce enough insulin (Type-I Diabetes) or doesn't properly use the insulin it produces (Type-II Diabetes) [2]. According to WHO report (2014), about 422 million people over the age of 18 were suffering from diabetes throughout the world [3] out of which type-II diabetes accounts for the vast majority of people around the world [2]. A common pathology shared among type II diabetic patients is the accumulation of islet amyloid polypeptide (IAPP, also known as amylin) in an insoluble fibrillar form in the pancreas [4]. Similar accumulations of misfolded amyloid proteins have also been found to be characteristic of other diseases that strike primarily late in life, including Alzheimer's, Parkinson's, and Huntington's diseases [1]. Self aggregation of human islet amyloid polypeptide (hIAPP) is associated with the development of type-II diabetes by the disturbance of cellular homeostasis in islet cells through the formation of oligomers [5,6].

## Discussion

Human islet amyloid polypeptide (hIAPP) or Amylin, is a small neuroendocrine polypeptide hormone (37 amino acid) secreted by pancreatic  $\beta$ -cells that form aggregates under insulin deficiency metabolic conditions. Accumulating data suggests that toxic aggregates of IAPP may contribute to  $\beta$ -cell dysfunction and disease [7,8]. More recently, it has been recognized that amylin deposits are actually present in more than 90% of type-II diabetes patients [9] hence these reports strongly suggest that these aggregates become a pathological hallmark of type-II diabetes. The important question is whether these aggregates act as inert bystanders that result due to tissue damage during the disease, or whether they play a vital role in type-II diabetes pathogenesis. For this many studies have been performed. One longitudinal study showed that formation of IAPP aggregates precede  $\beta$ -cell dysfunction and clinical signs of the disease in animal models that spontaneously develop type-II diabetes (non-human primates and domestic cats)[9]. Transgenic mice and rats over expressing human IAPP spontaneously developed clinical and pathological hallmarks of type-II diabetes [10].

Previously, the general notion was that the fibrillar form of amylin is toxic but the current consensus supports that the

oligomeric form of amylin exerts toxic effect [11]. The exact mechanism behind the amylin aggregates mediated destruction of beta cells was not clearly understood. There are various assumptions regarding its mechanism. The first mechanism is that amylin aggregates disrupt cell membrane and subsequent imbalance of intracellular homeostasis thereby causing pancreatic cell death [12]. The second mechanism demonstrates that amylin aggregates promote pores or channels formation in lipid bilayer [13,14] resulting cell death. These are the most accepted cytotoxic mechanisms of amylin aggregates. There are some other suggested mechanisms for amylin aggregates mediated cytotoxicity which includes an ER stress response [15], activations of stress-activated kinases [16] and induction of reactive oxidative stress species or radicals [17,18]. It is also possible that all these mechanisms could work together to result in cell death ultimately. On this basis, considering type-II diabetes as a protein misfolding disorder will open an entirely new area of research and uncover novel targets for therapeutic intervention.

### Conclusion

Amylin aggregation has been suggested to be toxic for pancreatic  $\beta$  cells. Destruction of these pancreatic beta cells results in decreased insulin production and manifests as type-II diabetes. Now these days, metformin and insulin are most commonly used treatment for diabetes. Although these two therapeutic agents help to manage the disease, they do not prevent progression nor do they cure the disease. The exact mechanism and factors implicated in the transition from pre-diabetic conditions to  $\beta$ -cell failure and type-II diabetes are still not clear. So we should divert our focus in discovering a permanent cure for type-II diabetes and targeting amylin aggregation may be an answer to this question.

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