

## Relationship Of Incidence Of Frailty With Metformin Consumption Habits In Elderly Type-2 Diabetes Mellitus Patients

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### ABSTRAK

Diabetes tipe 2 (T2DM) ditandai dengan resistensi dan defisiensi insulin, selanjutnya dengan bertambahnya usia juga terjadi peningkatan resistensi insulin. Studi klinis telah membuktikan bahwa resistensi insulin dan T2DM meningkatkan kejadian sindrom kelemahan pada orang tua. Antidiabetik oral metformin dikaitkan dengan penghambatan proses penuaan. Meskipun demikian, ada literatur dan teori tanpa batas yang menunjukkan hubungan terapi metformin dengan sindrom kelemahan. Penelitian ini bertujuan untuk mengeksplorasi kemungkinan efek perlindungan metformin pada sindrom kelemahan. Metode penelitian ini menggunakan analisis deskriptif terstruktur dengan tinjauan pustaka. Data artikel baik artikel asli, artikel penelitian, artikel Ulasan dan laporan kasus dikumpulkan untuk dianalisis sesuai dengan maksud judul dan penulisan artikel ini. Diabetes melitus Tipe 2 ditandai dengan resistensi dan defisiensi insulin yang telah terjadi beberapa dekade sebelumnya, selain itu insidensi resistensi insulin juga akan meningkat. Pada beberapa studi klinis yang telah dilakukan, resistensi insulin dan Diabetes melitus tipe 2 telah terbukti meningkatkan jumlah kejadian sindrom kelemahan pada usia lanjut. Kesimpulan Metformin terbukti memiliki efek perlindungan terhadap sindrom kelemahan pada penderita diabetes lanjut usia

**Kata Kunci** : Diabetes melitus, Frailty, Lanjut usia, metformin.

### ABSTRACT

Type 2 diabetes (T2DM) was characterised with insulin resistance and deficiency, furthermore with advancing age the was also an increase in insulin resistance. Clinical studies has proven that insulin resistance and T2DM increase the incidence of frailty syndrome in the elderly. Oral antidiabetics metformin was associated with the inhibition of aging process. Eventhough, there was limitless literature and theoretical that showed the relationship of metformin therapy to frailty syndrome. This study aimed to explore the possibility of metformin protective effect on frailty syndrome. This research method uses structured descriptive analysis with literature review. Article Data both original article, research article, Review article and case report are collected to be analyzed in accordance with the purpose of the title and writing of this article. Type 2 Diabetes mellitus is characterized by insulin resistance and deficiency which had happened several decades earlier, in addition to the incidence of insulin resistance will also increase. On some clinical studies that have been conducted, insulin resistance and type 2 Diabetes mellitus, it has been shown to increase the number of occurrences of frailty syndrome in old age. Conclusion Metformin was shown to have protective effect against frailty syndrome in elderly diabetic

**Keywords**: Type 2 diabetes , Frailty, Old age, Metformin

## **I. INTRODUCTION**

### **1. Introduction**

The aging process occurs at different rates, not the same as the chronological age in this process are found wide variations of individuals and organs. There are various factors that can affect the aging process, including spiritual psychosocial status, nutrition, physical activity, dietary patterns, chronic diseases and drugs(Allard *et al.*, 2008; Amaral, 2016). In addition, old age is also characterized by various comorbidities and impaired function. Among the comorbidities that significantly affect the aging process is insulin resistance and diabetes mellitus type 2 (DM2)(Caesari *et al.*, 2017). Epidemiological studies show that DM2 is one of the most common diseases suffered by usila. About 10% of the usila population known to suffer from DM2, while a number of the same suspected also suffer but not diagnosed(Magalhaes *et al.*, 2017). Diabetes in usila, is associated with a wide variety of morbidities, ranging from cardiovascular disease, stroke, kidney, infection and as well as violence. More recently, one of the features of the poor aging process, frailty, has been associated with DM2. Frailty itself, until now still cannot be defined with certainty, but frailty is considered as a state between autonomy and full dependency or death. The existence of a state of frailty in usila, which can also be considered as a result of accumulated deficits and various medical conditions, makes usila have a high risk of disability, hospitalization, hospitalization and death(Kalemci *et al.*, 2017). Type 2 Diabetes mellitus is characterized by insulin resistance and deficiency that has occurred several decades before, in addition, along with aging, the incidence of insulin resistance will also increase. In several clinical studies that have been conducted, insulin resistance and type 2 Diabetes mellitus, have been shown to increase the number of occurrences of frailty syndrome in usila(Dwipa *et al.*, 2021). Diabetes in usila has also been shown to increase the proportion of subjects with frailty, ranging from 22% in the general population to more than 40% in usila with Diabetes type 2 diabetes. Insulin resistance and prandial blood sugar dysregulation have been shown to be associated with one important component of frailty syndrome, sarcopenia(Charan *et al.*, 2013). Obesity, which is closely related to insulin resistance and Diabetes type 2 diabetes mellitus, also associated with the incidence of sarcopenia so that at this time also known as sarcopenic obesity. Oral antidiabetic drugs that increase sensitivity insulin such as metformin and thiazolidinedione have been associated with inhibition of the aging process in some laboratory studies. Data from animal studies, especially on fruit flies and nematodes, studies show that intervention with metformin can prolong life life between 40-200%. Similar results were also found in other experimental animals such as mice and rhesus macaques. While studies for thiazolidinedione so far, it has not shown consistent results(Bourdel and Berrut, 2014).

### **2. Research Problem**

This paper discusses how the role of the mechanism of Frailty in elderly patients suffering from Type-2 Diabetes Mellitus is associated with metformin consumption habits.

### **3. Research Purpose**

The purpose of writing this article is to describe the mechanism of metformin consumption on the incidence of frailty in elderly patients suffering from diabetes mellitus.

### **4. Research Benefits**

This paper is expected to be useful for researchers, health practitioners and medical teams as well as medical supporters in implementing and implementing metformin consumption

management against the incidence of frailty in elderly patients suffering from diabetes mellitus

## II. RESEARCH METHOD

The method used is an analysis and observative literature directly with the study and the study obtained adjust to the purpose and title of the article writing. The articles collected are articles from reliable and accredited sources so that they can be accounted for for the novelty and source of the data concluded. The data obtained were then analyzed in a qualitative follow-up to obtain a common thread and the appropriate scheme between the articles.

## III. RESULTS AND DISCUSSION

### RESULTS

This article shows that the concept of frailty began to arise as a distinct clinical syndrome a few years ago based on the experience of geriatricians. This concept very impressive despite the difficulties in providing a the exact definition of this term. The causes of Frailty syndrome are complex and should be accepted as a multidimensional relationship of genetic, biological factors, physical, social and environmental. The term frailty itself is often used in a way different according to the needs, but generally used for describe a physical and functional decline that can dimbul as result of certain diseases, but can also arise in the absence of disease specific recognisable. So frailty itself is considered a loss physiological reserve and endurance.



Picture 1. Frailty Syndromes

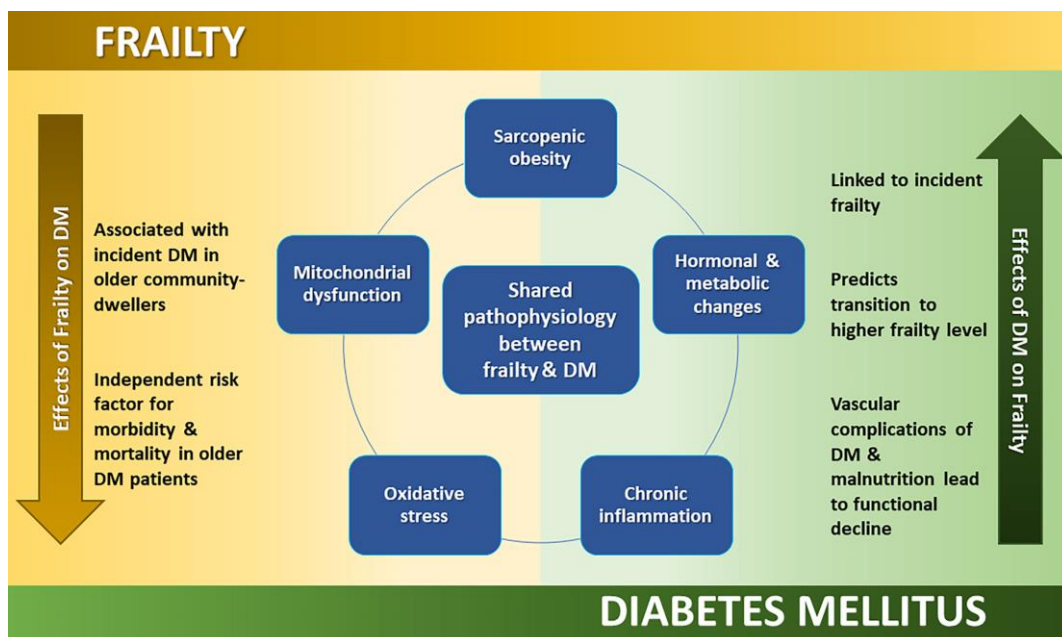
How to evaluate Clinical frailty debate. One of the definitions of the clinical syndrome of frailty according to Fried includes fatigue, decreased physical activity, slow walking speed, decreased strength grip and unwanted weight loss. Frailty considered to exist if found at least three of these characteristics, but thus the psychological, cognitive and social factors are also considered to play important role. Other methods for frailty evaluation using the frailty Index, which is calculated by assessing the presence of several (usually 40 or more) deficits potential. These deficits can be symptoms, signs, diseases, disabilities or abnormal lab results. The overall result of this accumulated deficit is, usila with frailty have a higher risk of cognitive decline, disability and death. The description above, actually provides an overview that the characteristics of frailty itself can be found in that aging process alone.

Thus, in terms of clinical practice, early identification the tendency to frailty can be useful to prevent or delay clinical consequences heavier ones. If there is a clinical diagnosis, it may be slow to perform effective interventions other than palliative.

## DISCUSSION

### Relationship Insulin resistance and diabetes mellitus with frailty

As already mentioned above, the most numerous criteria of CHS used to define frailty operationally enter some disability as a component of frailty (Lepereire *et al.*, 2012). Criteria such as decreased strength, unwanted weight loss, fatigue, low level of physical activity, low walking speed makes us have a high risk of experiencing falls, hospitalizations, disability and death. According to the Canadian Study of Health and Aging of 2,305 subjects over the age of 70 there is a strong link between diabetes and frailty. Subjects with diabetes 2.62 times more likely to suffer frailty (OR 2.62; 95% CI 1.36-5.06) regardless of age, gender and long suffering from diabetes. In addition, patients with diabetes also experience frail at a younger age compared with without diabetes (mean frail age 81.3 years vs. 83.3 years) (Casarotto *et al.*, 2019). Health study involving 2,895 subjects also studies show that individuals with diabetes experience increased risk for functional limitations compared non-diabetic (HR 1.5; 95% CI 1.3-1.7). Another study of Italian population, numbering 1,780, men and women 65 years and older, also shows the same, in which patients with diabetes experiencing frailty at a younger age (72.8 ° 5.8 years vs. 74.3° 6.4 years), have more domain disturbances (2.4 ± 1.5 domain vs. 1.95 ° 1.2), and increased mortality more high (93% vs. 36%, for every 1 point increase in the frailty Index) compared to non-diabetic (Jamshidi *et al.*, 2021).



Picture 2. Connection between Frailty and Diabetes mellitus

### Metformin as anti-aging therapy and potential Frailty syndrome.

The drug Metformin, which has recently been on the rise again, was found has a working mechanism that is able to regulate the AMPK pathway. On the level cellular, metformin activates AMPK, by interfering with the complex I chain mitochondrial respiration, Metformin lately in addition to functioning as an antidiabetic drug also found to have an effect on the suppression of cancer cells and also the process aging (Ingles *et al.*, 2019).

The effect of metformin is associated both with the direct effect (insulin-independent) and indirect (insulin-dependent) (Jose *et al.*, 2016).

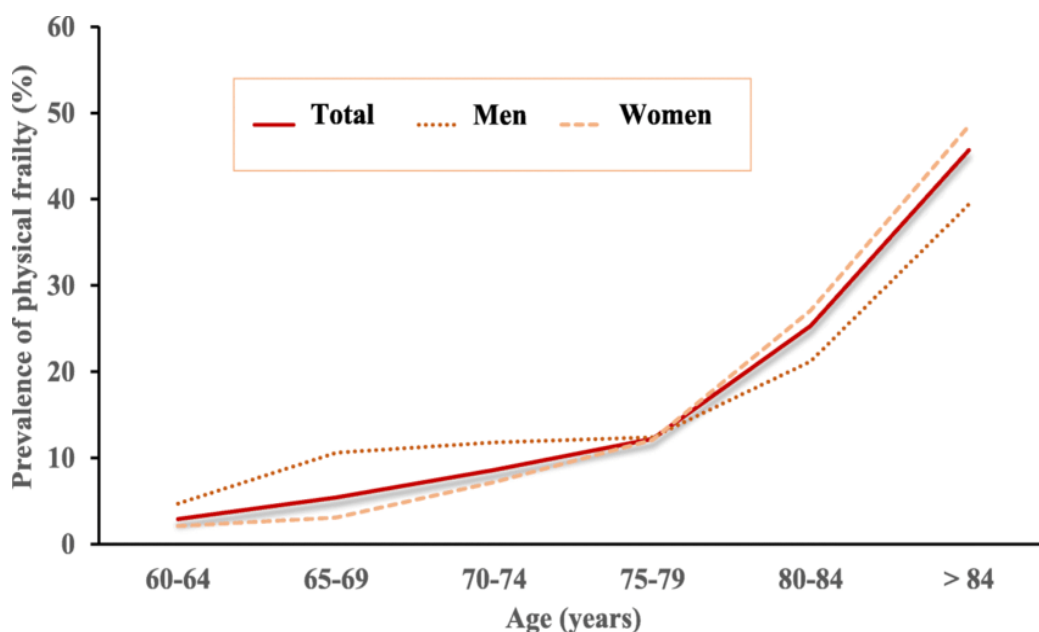
The effect is not directly, insulin-dependent is mediated by AMPK's ability to inhibit transcription of key gluconeogenesis genes in the liver and stimulates glucose intake in the muscles, thereby lowering fasting blood glucose levels and insulin. Insulin itself is known to have a paradoxical effect, namely on when the state of normo-insulinemia and good sensitivity, insulin has predominantly metabolic regulatory effect. But at the time of circumstances hyperinsulinemia and resistance, insulin is more mitogenic and advancing cell cycle progressivity (Ipson *et al.*, 2018).



Picture 3. Metformin HCl

#### IV. CONCLUSION

Several previous studies have reported that many molecules and signaling pathways are involved in the mechanisms underlying regulation. Metformin was shown to have a protective effect against frailty syndrome in elderly diabetics.



Picture 4. Estimated Prevalence Of Physical Frailty by age and sex

Frailty considered to exist if found at least three of these characteristics, but thus the psychological, cognitive and social factors are also considered to play important role. Subjects with diabetes 2.62 times more likely to suffer frailty (OR 2.62; 95% CI 1.36-5.06) regardless of age, gender and long suffering from diabetes. In addition, patients with diabetes also experience frail at a younger age compared with without diabetes.

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