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# The "skeletal muscle–fat" interplay in heart failure

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Independent from specific areas of commitment, the "obesity paradox" and the U-shaped mortality risk at the extremes of obesity in heart failure (HF) are well known principles in cardiovascular medicine.[1]

Indeed, this topic has typically generated intense controversy. First, body mass index (BMI), the most frequently used parameter for the definition of obesity, has been criticized for the inability to distinguish between fat and nonfat body composition. Nonetheless, targeted research has shown that both fat and nonfat body components independently affect cardiovascular outcome.[2]

## Adipose tissue and heart failure

Adipose tissue is an effective endocrine organ,[3] capable of secreting adipokines that have been implicated in HF and related cardiometabolic complications.[4] The underlying mechanisms have not been fully elucidated, but are likely to involve a complex interplay between inflammation, oxidative stress, impaired mitochondrial biogenesis, multiple paracrine and endocrine factors, insulin resistance with impaired glucose utilization, and functional and structural modifications of the vessel that precede the early stages of cardiac dysfunction.[5] In line with these considerations, markers of HF such as osteopontin[6] and osteoprotegerin are elevated in obesity.[7]

## Heart failure and skeletal muscle

A number of alterations in skeletal muscles have been described in HF including impaired $O_2$ utilization with reduced mitochondrial oxidative enzyme activity and volume density.[8] In addition, increased levels of circulating catecholamines, angiotensin II, arginine, vasopressin, and endothelin-1 induce enhanced vasoconstriction and reduced nitric oxide mediated vasodilation.[9,10]

## Adipose tissue, heart failure, and skeletal muscle

As previously mentioned, obesity is associated with a series of metabolic, inflammatory,[11] and hormonal changes,[12] which ultimately favors the incidence of HF. Conversely, data concerning skeletal muscles derive from models of already established HF.

Such observations have led us to perceive the link between HF and body composition in the following chronologic sequence: obesity increases the incidence of HF; the latter, perpetuated by obesity itself, induces skeletal muscle dysfunction with reduced mobility and increased morbidity, which further contributes to the maintenance of the vicious circle. In line with these considerations, nonintentional weight loss has been shown to be an independent predictor of mortality in HF patients.[13] Therefore, obese patients are collocated at the beginning of the observation period, which results in a relatively better prognosis when compared with lean patients.

On the other hand, these data appear in contrast with preventive medicine, historically attributing obesity with a negative impact on cardiovascular health. However, the "obesity paradox" has been mainly identified in individuals with low cardiorespiratory fitness.[14] Indeed, sedentary lifestyle negatively affects cardiocirculatory physiology, pulmonary gas exchange, and exercise tolerance.[15] Moreover,

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## Abbreviations

**BMI:** body mass index; **HF:** heart failure

aerobic exercise training with purposeful weight loss improves outcome in HF patients.[16] Therefore, these observations acknowledge that obese patients have a relatively worse prognosis.

## Conclusion

In conclusion, the feeling is that, when we adopt a "watchful attitude," obesity represents the "starting point" toward a negative cardiac outcome; conversely, when an "interventional attitude" with purposeful weight loss is adopted, the tendency can be inverted, with obesity being allocated relatively nearest to the negative outcome *(Figure 1)*. ■

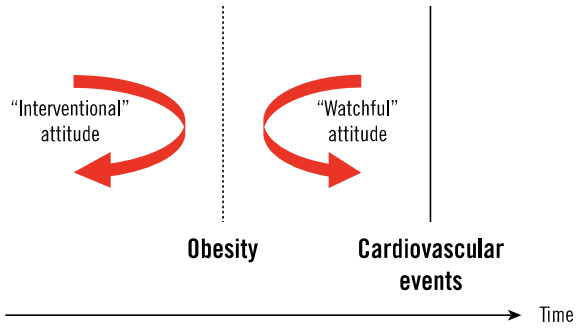


***Fig. 1*** *Illustration of the effects of an interventional attitude or a watchful attitude on cardiovascular events over time.*

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