

# Understanding the influence of obesity on the time course of pharmacological response

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## Introduction

- Obesity is a world wide epidemic (1)
- Dosing guidelines for patients who are obese are not available for most pharmacological agents
- No suitable size descriptor is available that helps to explain the influence of obesity on the pharmacological actions of drugs

## Objective

- To assess the influence of obesity on the time course of drug exposure
- **Lean Body Weight**
- The standard measure of lean body weight (LBW) was originally computed based on an analysis of three studies (2).
- Less than 10% of patients enrolled in these studies were obese
- The empiric formula although accurate for non-obese patients significantly under-predicts LBW for obese individuals (see Figure 1).
- We have recently developed a semi-mechanistic model for LBW (3) which accurately predicts actual lean body weight for patients from BMI=17 to 70 kg/m<sup>2</sup>

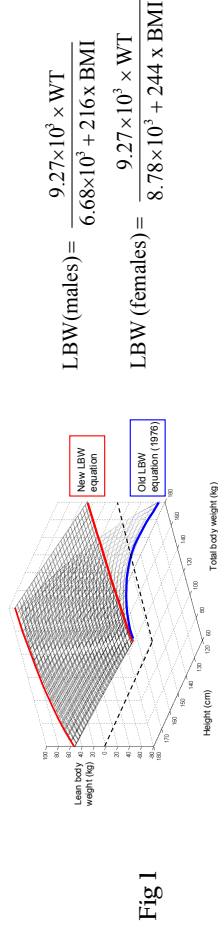


Fig 1

$$LBW(\text{males}) = \frac{9.27 \times 10^3 \times WT}{6.68 \times 10^3 + 216 \times BMI}$$

$$LBW(\text{females}) = \frac{9.27 \times 10^3 \times WT}{8.78 \times 10^3 + 244 \times BMI}$$

## The Lean Body Weight Hypothesis

LBW adequately predicts drug exposure by accounting for changes in body composition (4)

The LBW hypothesis includes three tenets that can be tested:

- Absolute clearance is greater in obese individuals
- Clearance increases non-linearly with WT
- Clearance correlates linearly with LBW

80 studies were identified in the literature which addressed clearance and obesity. All but three agreed with at least one tenet

## LBW to describe glomerular filtration rate (5)

- GFR data from a previous study at Tel Aviv University Medical School, Israel was re-analysed
- 9 subjects: Lean (BMI 20.1 – 24.6 kg/m<sup>2</sup>) 8 subjects: Obese (BMI 38.1 – 61.3 kg/m<sup>2</sup>)
- GFR was compared between lean and obese using repeated measures ANOVA (Figure 2)

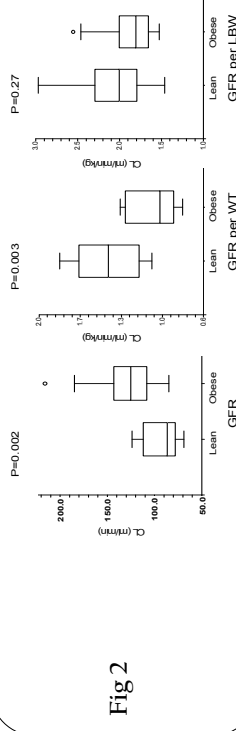


Fig 2

## LBW to describe High Hepatic Clearance (6)

- Hepatic clearance data were assessed by investigators at New York Medical College, USA
- 16 subjects: Lean (BMI 20.8 – 28.1 kg/m<sup>2</sup>) 10 subjects: Obese (BMI 30.9 – 54.1 kg/m<sup>2</sup>)
- Exclude liver or renal disease, and those requiring chronic analgesic medications
- Hepatic clearance was measured using fentanyl as a probe (Figure 3)

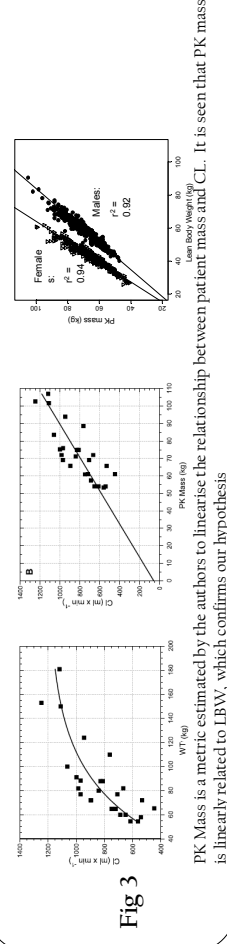


Fig 3

## Conclusions

- We believe that LBW is sufficient to explain the influence of body composition on CL
- Use of LBW as a covariate for CL in PK studies can enable quantitative predictions about the close-exposure-response relationship in the obese

## References

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