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Title: Klotho expression is reduced in COPD

Dr. Mehul S. 17092 Patel m.patel2@rbht.nhs.uk MD [1,2], Ms. Amy 17093 Lewis amy.lewis04@imperial.ac.uk [2], Dr. Samantha A. 17094 Natanek a.natanek@imperial.ac.uk MD [1,2], Dr. Dario 17095 Martolini martolini.dario@yahoo.it MD [1], Dr. Piet 17096 Bruijnzeel Piet.Bruijnzeel@astrazeneca.com MD [3], Mr. Vladimir 17098 Anikin V.Anikin@rbht.nhs.uk MD [1], Mr. Niall 17100 McGonigle N.McGonigle@rbht.nhs.uk MD [1], Mr. Simon 17101 Jordan s.jordan@rbht.nhs.uk MD [1], Dr. Nicholas S. 17097 Hopkinson n.hopkinson@rbht.nhs.uk MD [1], Dr. William D.-C. 17102 Man w.man@rbht.nhs.uk MD [1], Dr. Paul 17105 Kemp p.kemp@imperial.ac.uk [2] and Prof. Michael I. 17103 Polkey m.polkey@rbht.nhs.uk MD [1]. [1] NIHR Respiratory Biomedical Research, Royal Brompton Hospital and National Heart & Lung Institute, London, United Kingdom, SW3 6NP ; [2] Molecular Medicine Section, National Heart & Lung Institute, Imperial College, London, United Kingdom and [3] INR, AstraZeneca, Mölndal, Sweden .

Body: Introduction Klotho (KL) was discovered in transgenic rodents, mice deficient in KL develop sarcopenia and emphysema. KL is expressed both as a circulating hormone and a transmembrane protein. Limited data is available in COPD; where the quadriceps are particularly prone to dysfunction. Aims To assess the systemic and quadriceps expression of KL in COPD and healthy controls and to compare KL expression in the locomotor and respiratory muscles. Methods KL protein levels were determined from serum in 24 controls and 54 COPD patients and from vastus lateralis biopsies in 15 controls and 63 COPD patients. Other tests were FEV1%pred, fat-free mass index, quadriceps strength (QMVC/BMI) and six-minute walk. 12 COPD patients had vastus lateralis, external intercostal and diaphragm biopsies during routine thoracic surgery, sufficient protein was extracted from 12, 11 and 9 biopsies respectively. KL levels were log transformed, relationship to other parameters was assessed by Pearson's and differences by t-test or Kruskal-Wallis and post-test Dunn's. Results Serum KL (mean (SD)) was lower in COPD, 2.24 (0.19) v 2.38 (0.19); p=0.003. In COPD, serum KL weakly related to QMVC/BMI (r=0.33, p=0.02), but not with other parameters. Quadriceps KL did not relate to other measurements. Quadriceps KL was not lower in COPD, 1.56 (0.30) v 1.66 (0.37) p=0.27. Quadriceps KL 1.58 (0.22) was lower than intercostal KL (n=11) 1.86 (0.44); p<0.01 and trended to be lower than diaphragm KL (n=9) 1.76 (0.08). Conclusions Serum KL is reduced in COPD and relates to muscle strength. In COPD, the locomotor muscles express lower KL levels than the respiratory muscles; possibly due to different levels of chronic activation. KL may be involved in skeletal muscle adaptation in COPD.