Zonal Extracellular Matrix (ECM) Accumulation in Nonalcoholic Steatohepatitis (NASH) Characterized by a Mathematical Model of Fibrosis

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INTRODUCTION

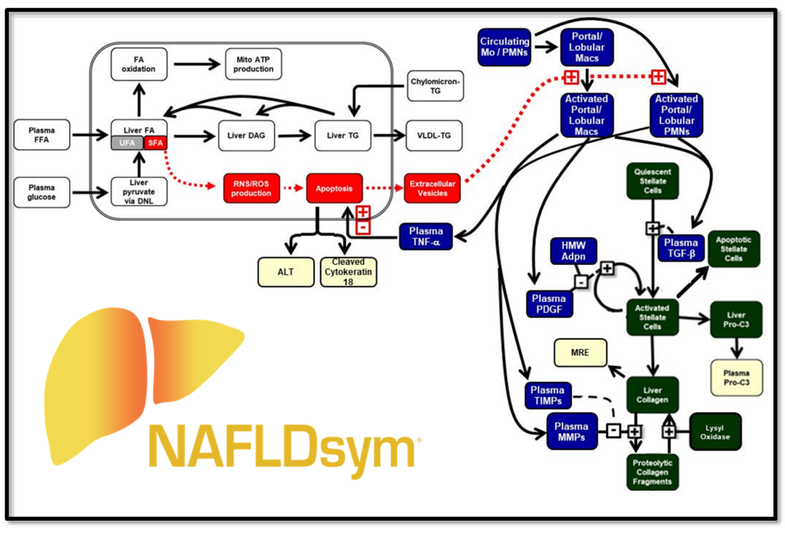
Non-alcoholic fatty liver disease (NAFLD) is of growing concern within developed countries, with recent estimates suggesting up to 30% of the US population may be affected[1]. NAFLD represents a spectrum of pathophysiology, ranging from hepatic steatosis, through non-alcoholic steatohepatitis (NASH) and hepatic fibrosis, and in rare cases resulting in cirrhosis and liver failure. Hepatic fibrosis in NASH is caused by excessive accumulation of extracellular matrix (ECM) proteins. Fibrosis progresses over time due to an increased number of activated hepatic stellate cells (HSCs) and subsequently increased production of hepatic ECM proteins. Fibrosis in NASH is histologically described by the accumulation of ECM in different hepatic acinar zones, with stage I fibrosis occurring in zone 3, stage II fibrosis expanding to zone 1, and stage III fibrosis bridging zones 1 and 3. This zonal pattern of ECM accumulation has not been captured in mathematical models of NASH fibrosis to date.

METHODS

A mathematical model of fibrosis was developed as a submodel within the NAFLDsym QSP model to represent dynamics of collagen turnover as well as zonal accumulation of collagen during the development of fibrosis in NASH. The model consists of a system of ordinary differential equations (ODEs) which describe the following processes in three discrete acinar zones of the liver: activated-HSC driven collagen I and III synthesis, MMP/TIMP modulation of collagen degradation, and collagen crosslinking by lysyl oxidase.

Collagen I and III synthesis rates and amounts were estimated across the stages of fibrosis using a combination of clinical studies measuring turnover of ^2H_2O-labeled collagen as well as collagen content from Elastica van Gieson-stained liver biopsy tissues in NASH patients[2,3]. The amount of collagen present across the stages of fibrosis was optimized by balancing the enzymatic activity of MMP/TIMP and lysyl oxidase. The spatio-temporal pattern of zonal collagen accumulation observed in histological scoring of fibrosis patients was captured by varying the Km of TGF-β driven activation of HSCs, with the Km increasing from the centrilobular (CL) to periportal (PP) to midlobular (ML) zones of the hepatic acinus.

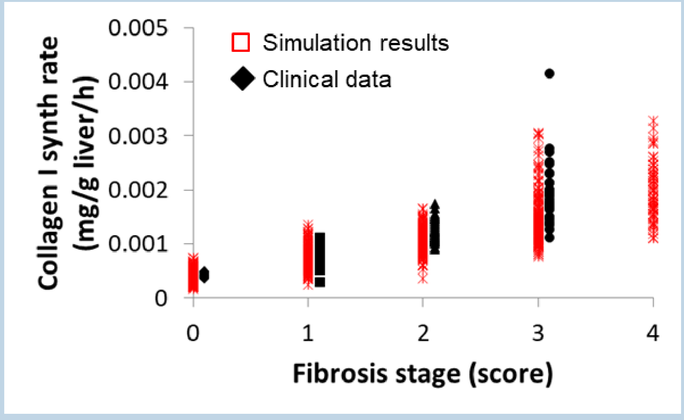
Variability in collagen synthesis rates and hepatic collagen content across stages of fibrosis was accounted for by the creation of a simulated population (SimPops®) which incorporated variability in parameters related to stellate cell activation and collagen synthesis/degradation, as well as other mechanisms related to the pathophysiology of NAFLD/NASH.

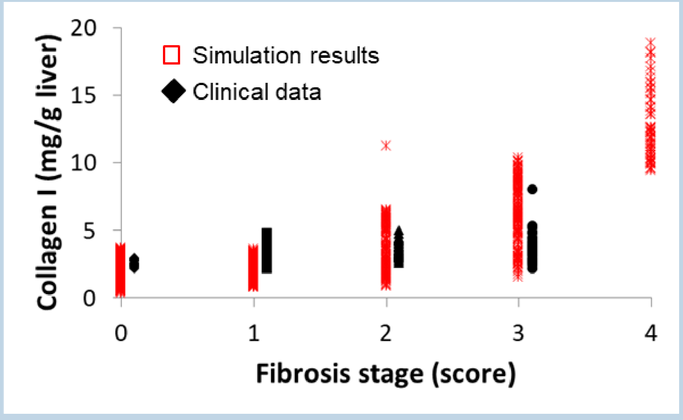


NAFLDsym QSP model. Components of the fibrosis submodel are shown in the green boxes.

RESULTS

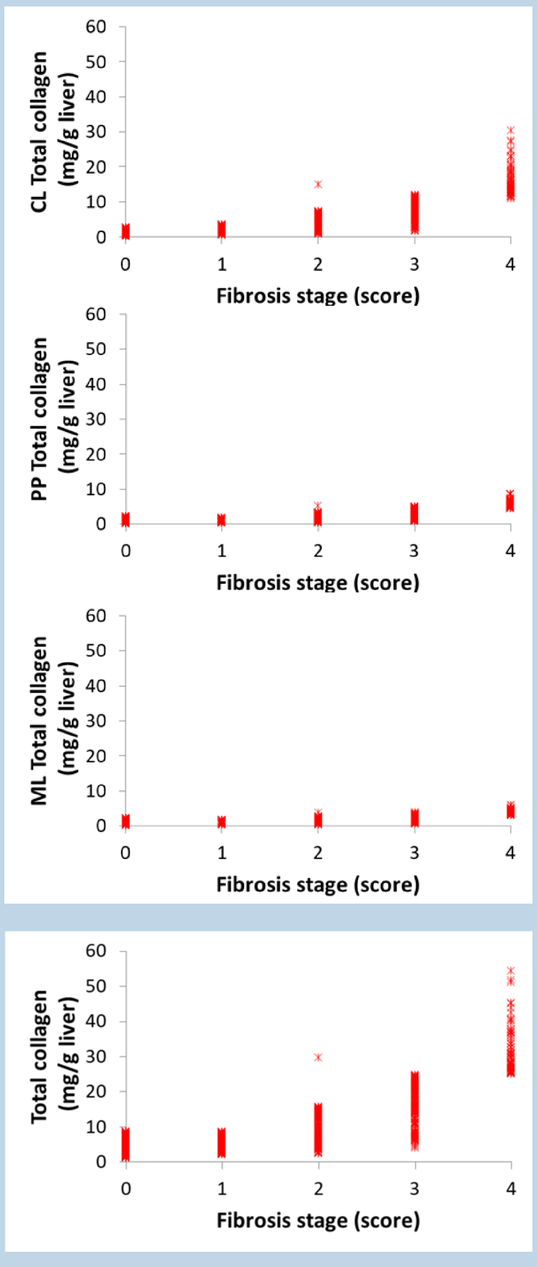
NAFLDsym Simulations Demonstrate Collagen Synthesis Rates and Levels Which are Consistent with Clinical Data

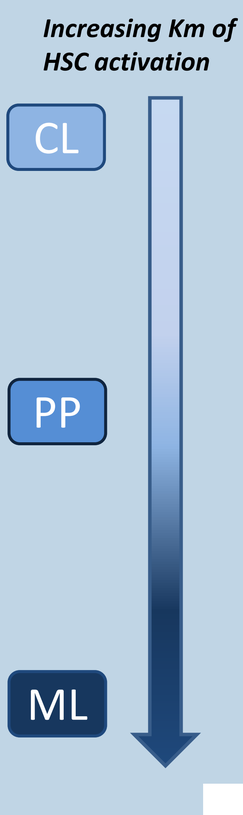




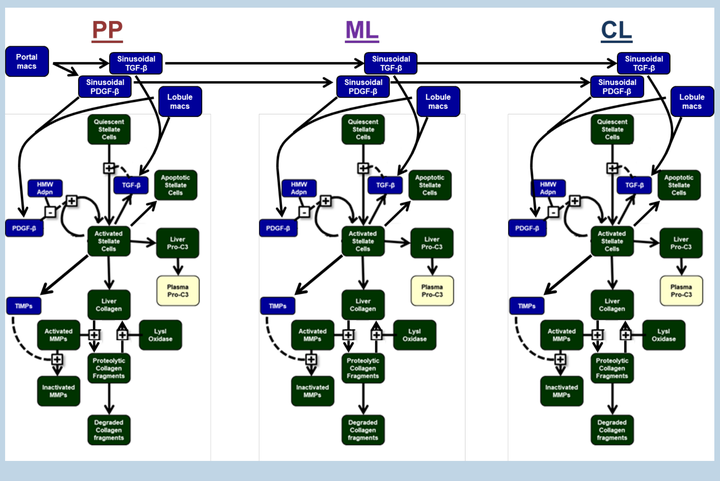
- Consistent with clinical data showing increased collagen synthesis rates in NASH patients, simulated rates of collagen I synthesis are greater in higher fibrosis stages[2].
- Rates of collagen III synthesis (not shown) are also predicted to be greater with higher fibrosis stages, however, clinical data on collagen III synthesis in NASH patients is not yet available for comparison.
- Simulated hepatic collagen I (shown above) and III (not shown) levels are comparable in fibrosis stages 0, 1, and 2, consistent with clinical data showing collagen levels in NASH patients[3].
- F3 and F4 collagen levels can dramatically exceed collagen levels seen in stages 0 – 2.

Zonal Activation of HSCs Results in Different Collagen Levels Across the Liver Acinus





- Histological scoring of hepatic fibrosis is based on the spatio-temporal pattern of collagen accumulation, with collagen first appearing in the centrilobular region, followed by accumulation in the periportal region of the acinus, and finally with the collagen bridging the centrilobular and periportal region as it accumulates in the midlobular region.
- NAFLDsym simulations accurately re-capitulate the zonal accumulation of collagen during progression of fibrosis.
- Simulated differences in zonal collagen accumulation observed between the centrilobular, periportal, and midlobular regions are driven by different Km values for TGF-β induced activation of hepatic stellate cells across the different zones.



CONCLUSION

- The integration of a mechanistic fibrosis submodel into the NAFLDsym QSP model accurately captures the zonal pattern of collagen accumulation in NASH-driven hepatic fibrosis and shows simulation results which are consistent with non-linear increases in hepatic collagen observed across fibrosis stages in NASH patients.
- A mechanistic mathematical model that captures the non-linear, spatially discrete increase in collagen which occurs during NASH progression while providing predictions which align with histologic scoring could serve as a useful tool to help guide development of therapeutics aimed at treating NASH.

REFERENCES

[1] McPherson et al. (2015) J Hepatol 62:1148-55.
[2] Decaris et al. (2017) Hepatology 65:78-88.
[3] Masugi et al. (2017) Hepatol Commun 27:58-68.

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