RECOMMENDATIONS

The results of the present study may have several future clinical implications:

- Further studies are needed to study the role of the oncogenic miR 17~92 cluster in the progression of chronic HCV infection to HCC.

- Clinical trials are required to assess the value of plasma levels of *MIR17HG* protein as a potential biomarker for HCV-related liver disease and as a non-invasive predictor of the severity of liver fibrosis.

- The effect of anti-viral therapy in modulating the miR 17~92 cluster in relation to the improvement in HCV-induced liver pathology needs to be evaluated.

- Future studies are required to assess the effects of the miR 17~92 cluster inhibitors on hepatic inflammation, steatosis and fibrosis in patients with chronic HCV infection.

- The use of PTEN mimics could be a promising therapeutic target for limiting inflammation, fibrosis and steatosis in HCV-related liver disease.

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الملخص العربي

كتلة الحمض النووى الريبوزى الصغير١٧~٩٢ وهدفه مماثل فوسفاتيز وتنسين (پيتن) فى العدوى المزمنة بفيروس الإلتهاب الكبدى سى

مقدمة البحث:

تعتبر الاصابة بفيروس الإلتهاب الكبدى "سي" من أهم أسباب حدوث الإلتهاب الكبدي المزمن والتليف الكبدى وسرطان الكبد. وعلى الرغم من ان العوامل التى تسهم فى استمرار الفيروس وتقدم مراحل الأصابة لم يتم بعد تحديدها فقد وجد أن الاصابة بالفيروس تؤدى الى حدوث تغيرات فى عدة مئات من الجينات، وهذا يؤثرعلى قدرة الجسم على التخلص من الفيروس وتقدم المرض.

الأحماض النووية الريبوزية "أ ن ر" الصغيرة هي عائلة من الأحماض النووية الريبوزية التى لا تكون بروتينات وتتراوح بين حوالي ٢١-٢٤ نيوكليوتيدات في الطول، وتلعب دورا رئيسيا في تنظيم التعبير الجيني في مرحلة ما بعد النسخ مما يؤدى إلى تثبيط الجينات، وقد تبين أن "أ ن ر" الصغيرة موجودة ليس فقط في الأنسجة ولكن أيضا تفرز من الخلايا ويمكنها الوصول إلى الدم، وبالتالى يمكن استخدامها كمؤشرات حيوية للكشف عن المرض. وعادة تتكون "أ ن ر" الصغيرة بشكل فردي وفى بعض الأحيان تتكون ككتلة مكونة من مجموعة من "أ ن ر" الصغيرة الفردية التى تنشىء من نفس النسخة الجينية.

تتكون كتلة "أ ن ر" الصغير ١٧~٩٢ من ستة من "أ ن ر" الصغيرة الفردية. ويلقب جين هذة الكتلة باسم "الچين المضيف "أ ن ر" الصغير-١٧". ومن المثير للاهتمام أن هذا الجين يستطيع نسخ بروتين مكون من ٧٠ حمض أميني يوصف بأنه "بروتين الچين المضيف "أ ن ر" الصغير-١٧" ويمكنه الوصول إلى الدم مثل "أ ن ر" الصغيرة. وتعمل كتلة "أ ن ر" الصغير ١٧~٩٢ كمنظم رئيسي لمجموعة واسعة من العمليات البيولوجية بما في ذلك تكاثر الخلايا والتمثيل الغذائي والإستجابة المناعية، والإستجابات الإلتهابية، وتكون الأوعية الدموية. كما وجد أن هذة الكتلة تنشط بصورة غير مباشرة العامل النووي كابا " بى" وهو أحد العوامل المسببة للإلتهابات. وتعمل كتلة "أ ن ر" الصغير ١٧~٩٢ على تثبيط العديد من الجينات منها مماثل فوسفاتيز وتنسين "پيتن". وقد وجد أن نقص "پيتن" في خلايا الكبد يؤدى الى التدهن الكبدى وتليف الكبد.

الهدف من البحث:

الهدف من هذا البحث هو تقييم مستوي بروتين الچين المضيف "أ ن ر" الصغير-١٧ فى البلازما واظهار "پيتن" فى الكبد في مرضى العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" وعلاقتهما بالتدهن والإلتهاب والتليف الكبدى.

حالات البحث:

اشتملت الدراسة علي ٣٠ من مرضي العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" الذين لم يسبق علاجهم، بعد منهم ١٨ مريضا مصابا بالإلتهاب الكبدي "سى" المزمن و ١٢ مريضا لديهم تليف بالكبد. وجميع المرضى لديهم اجسام مضادة للفيروس والحمض النووى للفيروس في الدم وتغييرات بأنسجة الكبد نتيجة العدوى المزمنة بالفيروس. كما اشتملت الدراسة على ١٥ من الأشخاص الأصحاء كعينة ضابطة. وقد استثنى من البحث المرضى المصابين بفيروس الإلتهاب الكبدى "بي" ومرض الكبد الناتج عن تناول الكحوليات أوالإصابة بالبلهارسيا، او غيرها من الاسباب المعروفة لأمراض الكبد المزمنة. كما تم استبعاد المرضى المصابين بارتفاع بدرجة الحرارة، أو الإلتهابات حادة، أو أورام سرطانية، أو أمراض قلبية أو صدرية أو كلوية أو أمراض مزمنة أخري مثل مرض السكري أو أمراض النسيج الضام أوالذين تلقوا علاجا للإلتهاب الكبدى "سى" المزمن.

خطة البحث و طرق الفحص:

اشتملت خطة البحث و طرق الفحص علي تقييم كل المرضى و الاشخاص الاصحاء كالاتى:

- الفحص الاكلينيكى الشامل مع التركيز علي مدة الإصابة الظاهرية بفيروس الإلتهاب الكبدى "سى" والأسباب المحتملة للأصابة والأعراض والمظاهر الاكلينيكية لمرض الكبد المزمن وحجم الكبد والطحال.

- الفحص باستخدام الموجات فوق الصوتية لفحص نمط صدى الكبد وتشخيص التليف الكبدي واستسقاء البطن وتضخم الطحال.

- الفحوصات المعملية و خاصة عد الدم الكامل و اختبارات وظائف الكبد [مستوى انزيمات الكبد (انزيم ناقل أمين الاسبارتات وانزيم ناقل أمين الألانين وانزيم ناقل جاما جلوتاميل) والالبومين والصفراء في مصل الدم ووقت البروثرومبين].

- قياس مستوي الحمض النووي لفيروس الإلتهاب الكبدي "سي" فى مصل الدم بإستخدام التفاعل التسلسلى بأنزيم البوليميريز.

- قياس مستوى بروتين الچين المضيف "أ ن ر" الصغير-١٧ فى بلازما الدم باستخدام طريقة الإنزيم المرتبط بالإمتصاص المناعى (ايليزا).

- اخذ عينات من الكبد من مرضي العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" وعمل الفحص الهستوباثولوجى للأنسجة لتحديد درجة النشاط الهيستولوجى ومرحلة التليف الكبدى حسب تقسيم ميتافير وكذلك تحديد درجة التدهن الكبدى.

- وقد تم صبغ عينات الكبد من المرضي باستخدام الصبغة المناعية الهستولوجية الكيميائية بواسطة الأجسام المضادة نحو "پيتن" والعامل النووي كابا " بى" وقد تم تقسيم درجة الصبغة المناعية كالأنى: "صفر" = عدم وجود صبغة بالخلايا، "١ " = ضعيف الصبغة، "٢ " = متوسط الصبغة، "٣ " = شديد الصبغة.

نتائج البحث:

أظهر التحليل الاحصائي للبيانات التى تم الحصول عليها من الدراسه الحالية النتائج التالية :

- الأعراض التى عانى منها المرضى كالتالى: ألم بالجانب الأيمن الأعلى من البطن في ١٦ (٥٣,٣٪) من المرضى بينما لم يعاني أيا من المرضى من اليرقان أوالاستسقاء أو نزيف سابق من الجهاز الهضمي.

- أظهر الفحص بالموجات فوق الصوتية للمرضى وجود تضخم بالكبد في ٦ (٢٠٪) من المرضى، بينما كان حجم الكبد طبيعي في ١٨ (٦٠٪) من المرضى ومنكمشا في ٦ (٢٠٪) من المرضى. ووجد لمعان بالكبد في ٦ (٢٠٪) من المرضى، بينما كانت درجة لمعان الكبد طبيعية في ١٤ (٤٦,٧٪) من المرضى ووجد تليف بالكبد في ١٠ (٣٣,٣٪) من المرضى. وكان هناك تضخم بالطحال في ١٢ (٤٠٪) من المرضى الذين كانوا جميعا يعانون من التليف الكبدي.

- اظهر متوسط مستوي انزيمات الكبد بمصل الدم ووقت البروثرومبين زيادة ذات دلالة احصائية في المرضى بالمقارنة بالأشخاص الأصحاء فى حين لم يظهراختلافا ذو دلالة احصائية فى تركيز الالبومين والصفراء في مصل الدم بين المجموعتين .

- تراوح مستوى الحمض النووي للفيروس في مصل الدم في مرضى العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" بين ٠٢,٠٠-٧٤٠٠٥×١٠^{٣} وحدة عالمية/ ملياتر بمتوسط ١٣٣٣.٥٢ ± ١٧٥٢.٤٠ ×١٠^{٣} وحدة عالمية/ ملياتر.

- وجدت زيادة ذات دلالة احصائية فى مستوى بروتين الچين المضيف "أ ن ر" الصغير-١٧ في بلازما الدم في مرضى العدوى المزمنة بفيروس الإلتهاب الكبدى "سى" بالمقارنة بالأشخاص الأصحاء. كما وجدت زيادة ذات

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رسالة علمية

مقدمة لكلية الطب – جامعة الإسكندرية
إيفاءاً جزئياً لشروط الحصول على درجة

الماجستير فى الأمراض الباطنة

مقدمة من

سـالي إسماعيل محمد الدميري

بكالوريوس الطب والجراحة

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كلية الطب
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سالي إسماعيل محمد الدميري
بكالوريوس الطب والجراحة
كلية الطب – جامعة الإسكندرية

للحصول على درجة

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لجنة المناقشة والحكم على الرسالة	**موافقون**
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التاريخ : ٣١ / ٣ /٢٠١٥

السادة المشرفون

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