肝硬変連携パス（医療者用）

肝硬変→肝がん
（病態進展予防）

医療機関		かかりつけ医	東京医科大学茨城医療センター
スケジュール		定期受診	☐ 3カ月後　　6カ月後　　年　　月　　日
達成目標		◎ 病院の治療方針に従って診察および検査を行い以下の項目を目標とする. ※ 腫瘍マーカーの増加がない ◎ 肝細胞がんがない ※ 肝機能の悪化がない	◎ 腫瘍マーカーの増加がない ※ 肝細胞がんがない ※ 肝機能の悪化がない ◎ 合併症がない
診察		◎ 自他覚症状の確認 ※ （倦怠感, 便の正常, 体重の変動など） ◎ 検査データの確認	◎ 自他覚症状の確認 ※ （倦怠感, 便の正常, 体重の変動など） ◎ 検査データの確認
検査	検体検査	◎ 肝機能検査（AST. ALT, gamma-GTP, Alb, T-bil） ◎ 血液一般（WBC, RBC, Hb, Plt）	◎ 必要に応じて検査を実施
	超音波	腫瘍マーカー（AFP, PIVKA-II）	※ 腹部超音波検査（原則3カ月まいに1回）
	画像		CTまたはMRI（造影）（原則6カ月または年に1回）
	その他		上部消化管内視鏡検査（原則年1回）
治療・処置		☐ 注射薬：強力ミノファーゲン　C ☐ 内服薬：ウルソ 　　　　　リーバクト顆粒	
指導		☐ 食事指導 ☐ 生活指導 ☐ 運動指導	◎ 食事指導 ◎ 生活指導 ◎ 運動指導
その他		☐ 報告書などの確認 ☐ 臨床症状・検査で異常所見がある場合は病院へ紹介	※ 紹介状などの確認 ※ 3カ月後または6カ月後の予約

肝硬変連携パス

☐ 対象症例
　肝硬変で分子鎖アミノ酸投与にてフォローする患者

☐ パスの目的
1) 病態の進展予防
2) 肝癌の予防および早期発見・治療
3) 合併症の把握と治療

☐ 基本原則
1) 病院への通院は, 3カ月または6カ月毎とする.
2) 検体検査について, 原則として保険診療範囲内で月1回かかりつけ医で実施する.
3) 超音波検査について, 原則として3カ月毎病院で実施する.
4) CTまたはMRIについて, 原則として6カ月または年1回病院で実施する.
5) 薬剤投与について, かかりつけ医が行うが, 年末年始や連休などは, 病院も適宜行う.
6) 他の合併症も含めた日常の管理は, かかりつけ医が行う.

検査の役割分担は, 病院, かかりつけ医との相談で決めることもある.

平成　　年　　月　　日
東京医科大学茨城医療センター消化器内科

この連携パス（診療計画表）は, 現時点で予想されるものであり, 症状に応じて変更になる場合があります.

肝硬変連携パス（患者様用）

肝硬変→肝がん
（病態進展予防）

医療機関		かかりつけ医	東京医科大学茨城医療センター
スケジュール		定期受診	☐ 3カ月後　　6カ月後　　年　　月　　日
診察		※ あなたの病状をかかりつけ医の先生にも連絡し, 病院主治医とかかりつけ医があなたの治療方針を共有して治療していきます.	※ 東京医大の外来にて現在の状態を確認するため, 診察を行います. ※ 担当医師から血液検査や画像診断の結果に関して説明があります.
検査		現在の状態を知るために以下の検査を行います ※ 血液一般検査 ※ 肝機能検査 ※ 腫瘍マーカー	※ 以下の検査を必要に応じて行います ※ 血液検査　血液一般検査, 肝機能検査, 腫瘍マーカー　など ※ 画像診断　腹部超音波　　CT検査　　MRI検査 ※ その他　上部消化管内視鏡検査
治療・処置		☐ 注射薬：強力ミノファーゲンC ☐ 内服薬：ウルソ, リーバクト	
指導		☐ 食べ過ぎに注意し, 肥満は避けましょう ☐ C型肝炎のかたは, 鉄分の取り過ぎを避けましょう ☐ 感染防止のため, ひげ剃り, 歯ブラシの共用はやめましょう ☐ アルコールはやめましょう ☐ 睡眠はしっかりとりましょう ☐ 入浴は, ぬるめにして, 長湯はよくないのでやめましょう	お薬や食事についてお聞きになりたいことがありましたら当院の担当医師にご相談ください.
症状		☐ 食欲がない・身体がだるい・腹部が張る ☐ 便の色が変化（黒色便） ☐ 体重のチェック ☐ その他	
その他		☐ 病状に変化があった場合は, かかりつけ医に相談しましょう	※ 再来受付機を通し, 　　窓口へ ※ 次回外来の予約票を受け取る

肝硬変連携パス

☐ 通院
定期受診はかかりつけ医で, 病院には3カ月または6カ月毎の受診です.

☐ 薬剤
内服薬・注射はかかりつけ医で行います.

☐ 検体検査
血液検査・肝機能検査・腫瘍マーカーは, かかりつけ医で行い, 病院は必要に応じて検査を実施します.

☐ 画像診断
画像診断は, 原則として病院で行います.
超音波検査：3カ月に1回
CTまたはMRI（造影）：6カ月または1年に1回
上部消化管内視鏡：6カ月に1回

☐ 食事
1日3食, 生活のリズムにあわせて規則的にとりましょう. また, タンパク質, 炭水化物, 脂肪をバランスよくとることが大切です.

☐ 生活
アルコールは原則禁止です
睡眠はなるべく1日7時間以上.

その他, かかりつけ医や担当医師の指示にしたがってください.
病状に変化があった場合はかかりつけ医に相談してください.

平成　　年　　月　　日
東京医科大学茨城医療センター消化器内科

この連携パス（診療計画表）は, 現時点で予想されるものであり, 症状に応じて変更になる場合があります.

図1　代償性肝硬変患者のための病診連携パス

慢性肝疾患フォローアップ手帳
～肝ガン撲滅を目指して～

イニシャル

性　別　　M・F

県南・県西肝疾患研究会　発行

この手帳は、慢性肝疾患のフォローアップにあたり、特に
C型肝炎インターフェロン治療などの効果判定や副作用を最小限
に抑えるため、さらに肝癌発症の予防並びに早期発見をはかる
ため、医師同士が連絡を取り合うためのものです。医療機関を受
診した際には必ず医師に見せてください。個人は特定できないよ
うに配慮してありますが、あなたの病状についての情報が収載さ
れておりますので、紛失しないように大切に保管してください。

MEMO

医療機関名

転院する場合は、主治医の先生と必ずご相談してください。

図2　慢性肝疾患フォローアップ手帳

普及までに小グループでの勉強会などを繰り返し開催するなどし，病診連携について賛同してくれるかかりつけ医を増やすことが必要であると考えている．

パスの形式に関しては，あまりに細かく整備されたものでは普及までのハードルが高いと考え，より簡単な形式のものを目指した．もともと，当院のある県南部，県西部の医療機関，とくにつくば市を中心とした医療ネットワークの創造を理念として，松﨑は「慢性肝疾患フォローアップ手帳」という冊子を作成し，これを病院，かかりつけ医で共有するというシステム作りを進めてきた（図2）．しかし，この方式は現在まであまり浸透したとはいえず，この手帳をもって受診する患者は少ない．病院や診療所での電子カルテやオーダリングシステムの普及により，検査データはプリントアウトされて患者に渡されることが多い昨今では，手帳にわざわざデータを記入するということが医療者側からすれば大きな負担になっている．また，かかりつけ医との約束事として分担する業務などについての

肝がん地域連携パス（術後）（医療者・患者さん共通）

当施設名：　　　　　担当医名：　　　　　連絡先 TEL：
連携施設名：　　　　担当医名：　　　　　連絡先 TEL：

患者情報

ふりがな	
患者氏名	様　男・女
生年月日	年　月　日

【退院時の状態】　（退院日　年　月　日）

今回の肝がんの状態

最大径	cm
個数	個
脈管侵襲	（有・無）
肝外転移	（有・無）
Stage	（ I・II・III・IV-A・IV-B ）

今回の肝がんの治療

検査

GOT	
GPT	
Alb	
T-Bil	
PT	
NH3	
AFP	
PIVKA-II	
HBs抗原	（ +・- ）
HCV抗体	（ +・- ）

投薬

注射

備考

※ 再発のない限り、下記スケジュールを継続します。

退院後	連携施設 1ヶ月	連携施設 2ヶ月	当施設 3ヶ月	連携施設 4ヶ月	連携施設 5ヶ月	当施設 6ヶ月
受診月日	月　日	月　日	月　日	月　日	月　日	月　日
検査	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II □腹部US・CT(MRI)	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II □腹部US・CT(MRI)
投薬	□投薬	□投薬		□投薬	□投薬	
注射(点滴)	□注射(点滴)	□注射(点滴)		□注射(点滴)	□注射(点滴)	
体重	□体重	□体重		□体重	□体重	

退院後	連携施設 7ヶ月	連携施設 8ヶ月	当施設 9ヶ月	連携施設 10ヶ月	連携施設 11ヶ月	当施設 1年
受診月日	月　日	月　日	月　日	月　日	月　日	月　日
検査	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II □腹部US・CT(MRI)	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II □腹部US・CT(MRI)
投薬	□投薬	□投薬		□投薬	□投薬	
注射(点滴)	□注射(点滴)	□注射(点滴)		□注射(点滴)	□注射(点滴)	
体重	□体重	□体重		□体重	□体重	

退院後	連携施設 1年1ヶ月	連携施設 1年2ヶ月	当施設 1年3ヶ月	連携施設 1年4ヶ月	連携施設 1年5ヶ月	当施設 1年6ヶ月
受診月日	月　日	月　日	月　日	月　日	月　日	月　日
検査	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II □腹部US・CT(MRI)	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II □腹部US・CT(MRI)
投薬	□投薬	□投薬		□投薬	□投薬	
注射(点滴)	□注射(点滴)	□注射(点滴)		□注射(点滴)	□注射(点滴)	
体重	□体重	□体重		□体重	□体重	

退院後	連携施設 1年7ヶ月	連携施設 1年8ヶ月	当施設 1年9ヶ月	連携施設 1年10ヶ月	連携施設 1年11ヶ月	当施設 2年
受診月日	月　日	月　日	月　日	月　日	月　日	月　日
検査	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II □腹部US・CT(MRI)	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II	□血算・肝機能 □AFP・PIVKA-II □腹部US・CT(MRI)
投薬	□投薬	□投薬		□投薬	□投薬	
注射(点滴)	□注射(点滴)	□注射(点滴)		□注射(点滴)	□注射(点滴)	
体重	□体重	□体重		□体重	□体重	

図3　高知県の肝がん地域連携パス

具体的な表示がなく，データと情報提供書を見れば把握ができる専門医間は別としても，非専門医とのやりとりには適していない．また，患者にとっても，次の受診予定などが明らかでないこと，自分の受けている診療内容について医師同士のやりとりが明らかになっていないなどの問題点がある．そこで，これらの反省点を踏まえて作成した連携パスは，①データ記入は行わないこと，②かかりつけ医，病院の役割を明確にすること，③診療スケジュールを明確にすること，を主眼としている．現在この連携パスはパイロットとして限定された医療機関と当院の間で運用中であり，改良を重ねて徐々に運用件数を増加させていきたいと考えている．

　他地域で開発され，実際に使用されている連携パスを示す．図3は高知県で使用されているものである[5]．肝がん術後患者用のバージョンを取り上げてあるが，基本的には治療終了後3カ月に1回は病院で画像検査を加え，その他の月はかかりつけ医で投薬，注射，体重チェックなどをうける，という流れはわれわれのものとほとんど同様である．形式として異なるのは，治療終了後から2年までを1枚にまとめていることである．連携パスが病院内で使用するパスと異なる点は，非常に長期にわたって使用されるケースが多いことが予想されることだが，長期にわたるそれぞれの診療スケジュールを患者に示しておくことにより安心感を持つものも多いかもしれず，繰り返し診療の要点を提示するのみでなく，今後の長期的な流れを理解してもらうことは

肝がん連携パス（医療者向け）　　　　　　　医療機関名 大坂府立成人病センター　　　　　　　　　　　　　　（診療録保存用）

患者情報

| カルテ番号 |
| 患者氏名　　　　　　　　　　　　　様　男・女 |
| 生年月日　　　年　　月　　日 |
| 　　　　病院　　科 |

【退院時の状態】　（退院日　　年　　月　　日）

今回の肝がんの状態

最大径	cm
個数	個
脈管侵襲	（有・無）
肝外転移	（有・無）
Stage	（Ⅰ・Ⅱ・Ⅲ・Ⅳ-A・Ⅳ-B）

今回の肝がんの治療

検査

ALT	
Alb	
T-Bil	
PT	
NH3	
AFP	
AFP-L3	
PIVKA-Ⅱ	
HBs抗原	（+・-）
HCV抗体	（+・-）

投薬
診療情報提供書に記載しています。

指導

日常生活指導	（済・未済）
脱薬指導	（済・未済）
栄養指導	（済・未済）

備考

	かかりつけ医	かかりつけ医	成人病センター	かかりつけ医	かかりつけ医	成人病センター
退院後	1ヶ月	2ヶ月	3ヶ月	4ヶ月	5ヶ月	6ヶ月
受診月日	月　日	月　日	月　日	月　日	月　日	月　日
検査	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ腹部US・CT(MRI)	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ腹部US・CT(MRI)
投薬	投薬	投薬	投薬	投薬	投薬	投薬
注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)

	かかりつけ医	かかりつけ医	成人病センター	かかりつけ医	かかりつけ医	成人病センター
退院後	7ヶ月	8ヶ月	9ヶ月	10ヶ月	11ヶ月	1年
受診月日	月　日	月　日	月　日	月　日	月　日	月　日
検査	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ腹部US・CT(MRI)	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ腹部US・CT(MRI)
投薬	投薬	投薬	投薬	投薬	投薬	投薬
注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)

	かかりつけ医	かかりつけ医	成人病センター	かかりつけ医	かかりつけ医	成人病センター
退院後	1年1ヶ月	1年2ヶ月	1年3ヶ月	1年4ヶ月	1年5ヶ月	1年6ヶ月
受診月日	月　日	月　日	月　日	月　日	月　日	月　日
検査	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ腹部US・CT(MRI)	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ腹部US・CT(MRI)
投薬	投薬	投薬	投薬	投薬	投薬	投薬
注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)

	かかりつけ医	かかりつけ医	成人病センター	かかりつけ医	かかりつけ医	成人病センター
退院後	1年7ヶ月	1年8ヶ月	1年9ヶ月	1年10ヶ月	1年11ヶ月	2年
受診月日	月　日	月　日	月　日	月　日	月　日	月　日
検査	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ腹部US・CT(MRI)	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ	血算・PT・肝機能（NH3・ビリルビン）AFP・PIVKA-Ⅱ腹部US・CT(MRI)
投薬	投薬	投薬	投薬	投薬	投薬	投薬
注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)	注射(点滴)

※ 再発のない限り、上記スケジュールを継続します。
検尿は必要時に実施をお願いします

図4　肝癌地域連携パス（大阪がん診療地域連携パス）

必要かもしれない.

　図4は大阪がん診療地域連携パスのなかの肝癌地域連携パスである[6]. 大阪府では，大阪府のがん診療連携拠点病院および14の地域連携拠点病院，大学付属病院，大阪府健康福祉部により協議会を構成し，5大がんについての連携パスについて，それぞれのがん別に検討班を立ち上げている. 特記すべきは，バリアンスと対処法についての記載があることであり，肝癌については，脳症，吐血・下血などの場合は救急病院へ紹介となっており，基本的には肝不全や肝硬変の合併症に関しては地域の病院に依頼するというスタンスをとっている（表1）. このパスは16病院が使用することになっているが，これらの病院にその他の大小の病院から紹介がなされ，治療が終わった患者はいったん紹介先に戻る，と

いった病病連携の構造のうえに成り立っており，肝硬変合併症などに対応できる救急病院などが多数ある大都市ならではというとらえ方もできる. このように多数の専門病院が軒を並べる大都市圏では，各専門病院が別々のパスを開発し，連携先に送付するということになると混乱を生じることになり，実際に現場で数多く使用されているインターフェロン投与のための病診連携パスでは，そのような現場の混乱もみられているようである. したがって，専門病院からは統一されたパスが提供された方がよいということになるが，その場合は拠点病院を中心とした，行政も巻き込んだ形でのシステム作りが必要になる.

4　まとめ

　がん診療連携は，患者に対してより質の高

表1 「肝がん連携パス」について

1. 対象患者について
　肝がん連携パスの対象患者さんは，原則として以下のすべてを満たす方としています.
・肝がん治療後
・肝機能不良例（Child C）を除く
・告知済み
・初発・再発は問いません.

2. 診療していただく時期
　退院後，できるだけ早い時期に.
　　（退院後，数日から2週間以内）

3. かかりつけ医の先生の診療時
　初回診療時には，患者さんに以下のものを持参していただきます.
　　・肝がん連携パス（医療者向け）・診療情報提供書・その他の資料
　診療時には血液検査（月に1回以上）と投薬，また必要な場合は注射もお願いします.
血液検査の項目は連携パスに記載の項目を含むようにお願いいたします.
　なお，患者さんには「肝がん連携パス」（患者用手帳）を渡しております. 心配なことが
あれば，かかりつけ医の先生に相談するように伝えておりますので，よろしくお願
い申し上げます.

4. 専門病院受診の前に
　可能でしたら，成人病センター定期受診（3カ月ごと）の前の診療時に診療情報提供書を
記載していただき，患者さんに渡してください.

5. バリアンスと対処法

バリアンス	対処法
再発が疑われるとき （腫瘍マーカーの持続的上昇）	2週間をめどに成人病センターを受診
腹水のコントロール不良	利尿剤の増量でもコントロール困難な場合はかかりつけ医を受診
肝性脳症	かかりつけ医である救急病院か，かかりつけ医から救急へ紹介してもらってください.
吐血・下血	かりつけ医である救急病院か，かかりつけ医から救急へ紹介してもらってください.

6. その他
・投薬につきましては，基本的にかかりつけ医の先生にお願いしています.

い適切な医療をきめ細かく提供することを目的に行政が後押しする形で推進されてきた. 2010年からの診療報酬改定では，がん診療連携パスに関する「がん治療連携計画策定料」（がん診療連携拠点病院など）と「がん治療連携指導料」（診療所）が新たに評価されたことから，連携パスの整備に取り組む施設が増加するものと思われる. しかし，ひとことでがん診療といっても，さまざまな状態の患者が存在し，どのレベルまでその地域で病院とかかりつけ医が役割分担できるのかは，やはり地域としてがん患者を診療するという機運が高いかどうかということで大きく変わってくる. かかりつけ医が気軽に専門医に問い合わせたり相談できたりする関係を構築することが重要であり，専門医とかかりつけ医の連絡

会を定期的に開催する，また，2者の関係を調整するコーディネーターのような職種が存在することが必要になろう．

根治性の高い他の癌と異なり，再発，肝機能の低下などのリスクが高い肝細胞癌の診療においては，いったん治療が開始されると専門医の診療が主体になるケースが通常であるが，ハイリスク群の早期発見のサーベイランス，発癌，再発予防のための診療に病診連携が有用であり，とくに専門医の少ない地域において非専門医の介入を促す必要があり，連携パスはその質を担保するためのツールとして積極的に利用する意義がある．また，都市部など医療機関が豊富な地域では，専門病院への患者集中を避けながら，患者が安心してかかりつけ医に通院できるようなシステム構築のツールとして連携パスを利用する意義がある．いずれにしても，各地域の実態や病診連携の成熟度に応じてパスが構築されるべきである．

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Original Article

Hepatitis C virus infection causes hypolipidemia regardless of hepatic damage or nutritional state: An epidemiological survey of a large Japanese cohort

Teruo Miyazaki,[1,2] Akira Honda,[1,2,3] Tadashi Ikegami,[3] Yoshifumi Saitoh,[3] Takeshi Hirayama,[3] Takashi Hara,[4] Mikio Doy[5] and Yasushi Matsuzaki[1,3]

[1]Department of Development for Community Medicine, Tokyo Medical University, [2]Center for Collaborative Research, [3]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Tokyo Medical University Ibaraki Medical Center, [4]Ibaraki Prefectural Institute of Public Health, Mito, and [5]Ibaraki Prefectural Central Hospital, Kasama, Japan

Aim: Infection with hepatitis C virus (HCV) is the leading cause of liver cirrhosis that develops into hepatocellular carcinoma. Previous studies have shown *in vitro* that lipids within hepatocytes are crucially important for a series of HCV infection–proliferation–release processes. On the other hand, in the patients with HCV, the serum total cholesterol (Total-C) and low-density lipoprotein cholesterol (LDL-C) levels have been reported to be lower. We conducted an epidemiological survey of a large cohort and investigated whether the lower serum lipid levels were caused by a direct or the secondary effects of HCV infection (i.e. hepatic damage or nutritional disorder).

Methods: Among 146 857 participants (male, 34%; female, 66%) undergoing public health examinations between 2002 and 2007 in Ibaraki Prefecture, Japan, the HCV positive rates determined by HCV antibody/antigen and/or RNA tests were 1.37% and 0.67% in males and females, respectively.

Results: In addition to Total-C and LDL-C, serum high-density lipoprotein cholesterol and triglyceride concentrations were also significantly lower in the HCV positive subjects compared with the negative subjects, regardless of sex, age or nutritional state evaluated by body mass index. Multivariate analysis showed that HCV infection was the strongest among the factors to be significantly associated with the lower level of these lipids. Particularly, the hypolipidemia was also confirmed in the HCV positive subjects with normal aminotransferase levels (alanine aminotransferase ≤30 and aspartate aminotransferase ≤30).

Conclusion: This epidemiological survey in a large Japanese cohort suggests that the HCV infection itself might directly cause hypolipidemia, irrespective of host factors including age, hepatic damage and nutritional state.

Key words: health examination, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglyceride

INTRODUCTION

H EPATITIS C VIRUS (HCV) infection is the leading cause of liver cirrhosis and the consequent development of hepatocellular carcinoma over time. The World Health Organization (WHO) estimates that there are approximately 180 million HCV carriers worldwide, namely, 3% of the world population, with 3–4 million new cases appearing every year, 70% of whom develop chronic hepatitis.[1,2]

Previous studies have shown that the life cycle of HCV is strongly associated with host lipids. The HCV forms lipo-viro-particles that are transported into hepatocytes via the low-density lipoprotein (LDL) receptor.[3–6] The replication of HCV occurs where the viral replicase is assumed to localize, on the phospholipid membrane of the endoplasmic reticulum (ER) or ER-associated membrane matrix.[7] The dynamic movement of lipid droplets to the ER has been confirmed to be involved in the production of HCV particles through core protein recruitment of non-structural proteins and in some steps of virus assembly.[8] Furthermore, HCV secretion from hepatocytes is closely associated with triglyceride (TG)-rich very low-density lipoproteins.[9–11]

Several epidemiological cohort studies reported that the serum total cholesterol (Total-C) and LDL cholesterol (LDL-C) levels in HCV carriers were significantly lower than those in uninfected control subjects.[12,13] Although the reason has not been elucidated, the lower levels of serum Total-C and LDL-C were specific in HCV carriers, but not in hepatitis B virus carriers.[14–18] Recently, we have estimated that the associated parameters in the public health examination for the HCV infection based upon multivariate analysis of data from over 25 000 individuals.[19] In the result, the greatest two negatively-associated parameters for HCV carriers were serum levels of Total-C and TG, while the most positively-associated parameters were serum aminotransferase levels. Here, a question has arisen whether the hypolipidemia in the HCV carriers was caused by the impaired liver function or not, because the liver is the central organ in lipid metabolism and the decreased level of serum cholesterols has been observed in the patients with liver cirrhosis due to lower ability of cholesterol synthesis and/or malnutrition.[20,21] However, previous studies have not shown whether the hypolipidemia would occur in asymptomatic HCV carriers with normal aminotransferase levels.[22–24] Furthermore, the effects of other factors, including age, sex, nutritional state and past history of HCV infection, on serum lipid levels have not been studied in HCV carriers.

In the present study, we investigated the relations between the serum lipid profiles and the above host factors in a large cohort in public health examination with over 140 000 participants including significant numbers of asymptomatic HCV carriers without any therapies. The results showed that the hypolipidemia was a characteristic feature in HCV carriers irrespective of aminotransferase levels or nutritional states.

METHOD

Cohort study and population

THE HCV TESTING was conducted during the annual public health examination for community residents, based in part on a project for urgent comprehensive countermeasures against hepatitis and hepatocellular carcinoma at the ages of 40, 45, 50, 55, 60, 65 or 70 years, from 2002–2006, and was supported by the Japanese Ministry of Health, Labor and Welfare. Additionally, the Ibaraki Prefecture extended the project of HCV testing for an additional year to 2007,

and the present study used data from a 6-year period. The present cohort study used the data from a total of 146 857 individuals (50 399 males, 34%; 96 458 females, 66%) who participated in the annual public health examinations from 2002–2007 in Ibaraki Prefecture. The HCV test was conducted with HCV antibody/antigen and/or RNA testing in accordance with the guideline for the medical HCV examination, as summarized in our previous report.[19] In the flow chart for the determination of HCV infection, using a cut-off index (COI) of the HCV antibody titer obtained with the HCV antibody test (Lumipulse; Fujirebio, Tokyo, Japan), subjects were initially divided into the HCV negative with COI of less than 1, the HCV positive candidates with COI of $1 \leq COI < 50$ and the HCV positive with COI of 50 or more. The HCV positive candidates were finally determined to be HCV negative and positive based upon the HCV antigen test for the HCV core protein and the nucleic acid amplification test (NAT) for HCV RNA.

The health examination involved measurements of serum lipid levels, including Total-C, high-density lipoprotein cholesterol (HDL-C) and TG, as well as age, height, weight and serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). According to the general health examination, serum was collected on fasting. Serum LDL-C levels were calculated using the Friedewald formula, as follows: LDL-C (mg/dL) = Total-C (mg/dL) – HDL-C (mg/dL) – 0.2 × TG (mg/dL).[25] Over 802 mg/dL (8.8 mmol/L) of TG level was excluded from the calculation of LDL-C.[26] The lipid levels were diagnosed as indicating normal, hypolipidemia or hyperlipidemia based on the respective reference value for Japanese clinical laboratory examination.[27,28] Body mass index (BMI) was calculated by dividing the weight (Wt) in kilograms by the square of the height in meters.[29] All of the health examinations, including HCV tests and serum biochemical analyses, were conducted in the Ibaraki Health Service Association and Ibaraki Prefectural Institute of Public Health (Mito, Japan), and the data of health examination were analyzed anonymously, after informed consent was obtained from community representatives to conduct an epidemiological study based on the guidelines of the Council for International Organizations of Medical Science.[30]

Classification by factors

In the present study, both HCV negative and positive subjects were further divided into subgroups based upon different factors: (i) sex; (ii) age; (iii) serum HCV

antibody titer; (iv) serum markers of liver damage; and (v) nutritional state. The age classification was established by the age range, and was divided into 5-year increments. In the classification by serum HCV antibody titer, the HCV negative subjects were divided into two subgroups, HCV antibody titer COI of less than 1 and COI of 1 or more, and the subjects with COI of 1 or more were finally decided as being HCV negative by the HCV antigen test and NAT.[19] For classification by liver damage, the HCV negative and positive subjects were further divided into the two groups, based upon the healthy limits of serum aminotransferases (ALT and AST): "normal" was less than 30 IU of both, and "abnormal" was over 30 IU of either or both aminotransferases. In Japan, the healthy limits of both serum aminotransferase levels for diagnosis of liver damage in public health examinations were re-established to be under 30 IU, based on the recent guideline for antivirus therapy for HCV.[31] The nutritional status was evaluated by BMI, and the classification was conducted along with the WHO-defined BMI class: under Wt was BMI of less than 18.5, normal Wt of $18.5 \leq BMI < 25$, over Wt of $25 \leq BMI < 30$ and obese class according to obese classes 1–3 (BMI >30).

Statistical analysis

Data are expressed as the mean ± standard error of the value or percentage. Significant differences between the two groups were determined by unpaired Student's *t*-test or Mann–Whitney *U*-test depending upon the number of subjects and variations in the groups compared. Comparison of the percent distribution between the two groups was estimated by Pearson's χ^2-test analysis. Multivariate logistic regression analysis was performed to determine factors including HCV positive, age, BMI, ALT and AST associated with serum level of each lipid diagnosed as the hypolipidemia (Total-C ≤ 119 mg/dL, HDL-C ≤ 39 mg/dL in males and ≤ 44 mg/dL in female, LDL-C ≤ 64 mg/dL, TG ≤ 49 mg/dL). The strength of association was described with an odds ratio with 95% confidence intervals and *P*-value. The statistical analysis was performed using SPSS II software version 11.0.

RESULT

HCV positive rate and profile of serum lipids between HCV positive and negative

AMONG THE 146 857 individuals who participated in the health examination from 2002–2007, the HCV positive rates were 0.90%, 1.37% and 0.67% in all

(sum of the sexes), males and females, respectively. There were no significant differences in BMI between the HCV negative (male, 23.9 ± 0.01; female, 23.1 ± 0.01) and positive (male, 23.3 ± 0.1; female, 23.1 ± 0.1) subjects. Table 1 shows the average serum lipid levels (Total-C, HDL-C, LDL-C and TG) by sex between the HCV positive and negative subjects. Among all subjects, all serum lipids in the HCV positive subjects were significantly lower than in the HCV negative subjects, regardless of sex.

The lipid levels in both HCV negative and positive subjects were divided into hypolipidemia, normal lipid and hyperlipidemia, based upon whether they were below, within and above the normal ranges of the respective reference values for Japanese (Fig. 1). Among both sexes, the proportion that were above the normal range for all examined lipids was significantly lower in the HCV positive compared to those in the HCV negative subjects (χ^2-test analysis $P < 0.0001$ in all: Total-C, 29% in the HCV negative vs 6% in the HCV positive for males, 41% vs 21% in females; HDL-C, 3% vs 1% in males, 6% vs 4% in females; LDL-C, 24% vs 7% in males, 34% vs 20% in females; TG, 35% vs 18% in males, 21% vs 14% in females).

The HCV negative subjects were also divided into those with HCV antibody titer of 1 or more and less than 1, and the former and latter were considered as having a prior infection and never infected.[17] The percentages of HCV negative subjects with prior infection were 0.91%, 1.28% and 0.72% for all, males and females, respectively, and the number of subjects was similar to the HCV positive subjects for each sex. Significant differences in the serum lipids were observed when the HCV positive subjects were compared regarding the presence or absence of a prior infection (Table 1). Among the HCV negative subjects, the examined lipids tended to be lower in those with prior infection compared with those who had never been infected, particularly in males, but there were no statistically significant differences.

Table 2 shows the multivariate logistic regression analysis of risk factors for lower level of serum lipids. In the parameters including HCV positive, age, ALT, AST and BMI, the significances were recognized in almost all analyses for the respective lower level of serum lipids in both sexes, while there were no significances in age for Total-C in male, ALT and BMI for Total-C in female, and both aminotransferases for LDL-C in female. In the HCV positive parameter of both sexes, the odds ratios in all examined lipids were remarkably higher than other analyzed

Table 1 Profile of serum lipids between the HCV negative and positive subjects by sex

	Total-C (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)
All				
HCV positive (n = 1317)	179.2 ± 1.0	52.9 ± 0.4	105.2 ± 0.3	107.6 ± 1.9
HCV negative (n = 145 540)	209.3 ± 0.1 **	60.3 ± 0.04 **	124.3 ± 0.1 **	124.5 ± 0.2 **
Titer ≥1 (n = 1326)	204.2 ± 1.0 **	57.3 ± 0.4 **	121.6 ± 0.9 **	127.5 ± 2.2 **
Titer <1 (n = 144 214)	209.4 ± 0.1 **	60.3 ± 0.04 **	124.3 ± 0.1 **	124.5 ± 0.2 **
Male				
HCV positive (n = 679)	168.1 ± 1.2	48.3 ± 0.5	98.0 ± 1.1	112.0 ± 3.1
HCV negative (n = 49 720)	202.1 ± 0.2 **	54.9 ± 0.1 **	118.3 ± 0.1 **	155.7 ± 0.5 **
Titer ≥1 (n = 638)	195.4 ± 1.3 **	53.3 ± 0.6 **	114.7 ± 1.3 **	139.3 ± 3.5 **
Titer <1 (n = 49 082)	202.3 ± 0.2 **	54.9 ± 0.1 **	118.4 ± 0.1 **	155.9 ± 0.5 **
Female	(vs male)	(vs male)	(vs male)	(vs male)
HCV positive (n = 638)	191.0 ± 1.4 (**)	57.8 ± 0.6 (**)	112.8 ± 1.2 (**)	102.9 ± 2.3 (*)
HCV negative (n = 95 820)	213.0 ± 0.1 ** (**)	63.1 ± 0.1 ** (**)	127.3 ± 0.1 ** (**)	113.3 ± 0.2 ** (**)
Titer ≥1 (n = 688)	212.4 ± 1.3 ** (**)	61.0 ± 0.5 ** (**)	128.1 ± 1.2 ** (**)	116.5 ± 2.5 ** (*)
Titer <1 (n = 95 132)	213.0 ± 0.1 ** (**)	63.1 ± 0.1 ** (**)	127.3 ± 0.1 ** (**)	113.2 ± 0.2 ** (**)

The titer ≥1 and <1 show the HCV negative subjects with HCV antibody titer over 1 and more, and less than 1, respectively. Data are shown the mean ± standard error. Significant differences between the HCV positive and HCV negative subjects and between sexes were analyzed by Mann–Whitney U-test. $*P < 0.05$, $**P < 0.0001$. Symbols in the parenthesis in female show the significant difference compared to that in male. LDL-C value was calculated using the Friedewald formula (LDL-C = Total-C – HDL-C – TG / 5).
HCV, hepatitis virus C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Total-C, total cholesterol.

Table 2 Multivariate logistic regression analysis of factors associated with hypolipidemia

	Total-C			HDL-C			LDL-C			TG		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Male												
HCV (+)	10.75	7.00–16.50	<0.0001	3.09	2.55–3.74	<0.0001	2.10	1.62–2.72	<0.0001	3.17	2.37–4.26	<0.0001
Age (years)	1.01	0.99–1.03	0.1180	1.02	1.01–1.02	<0.0001	0.98	0.99–0.99	<0.0001	0.99	0.98–0.99	<0.0001
ALT	1.01	1.01–1.02	<0.0001	0.98	0.98–0.99	<0.0001	1.04	1.04–1.05	<0.0001	1.02	1.02–1.02	<0.0001
AST	1.00	0.99–1.00	0.1870	1.02	1.01–1.02	<0.0001	0.98	0.98–0.99	<0.0001	0.96	0.96–0.97	<0.0001
BMI	0.89	0.85–0.94	<0.0001	1.15	1.14–1.16	<0.0001	0.95	0.94–0.97	<0.0001	0.80	0.78–0.81	<0.0001
Female												
HCV (+)	14.93	6.90–32.27	<0.0001	2.24	1.81–2.78	<0.0001	3.67	2.40–5.63	<0.0001	1.38	1.00–1.99	0.0479
Age (years)	0.94	0.92–0.96	<0.0001	1.03	1.03–1.03	<0.0001	0.93	0.93–0.94	<0.0001	0.94	0.94–0.94	<0.0001
ALT	1.02	1.00–1.04	0.1034	0.98	0.98–0.99	<0.0001	1.01	1.00–1.02	0.0566	1.03	1.03–1.04	<0.0001
AST	0.99	0.97–1.01	0.4201	1.02	1.01–1.02	<0.0001	1.00	1.00–1.01	0.5252	0.96	0.96–0.97	<0.0001
BMI	0.88	0.82–0.94	0.0002	1.13	1.12–1.14	<0.0001	0.96	0.94–0.97	<0.0001	0.84	0.84–0.85	<0.0001

The lower level of each serum lipid was defined as below the normal range of the respective reference value for Japanese, and see Figure 1 for the values.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HCV (+), positive for hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TG, triglyceride; Total-C, total cholesterol.
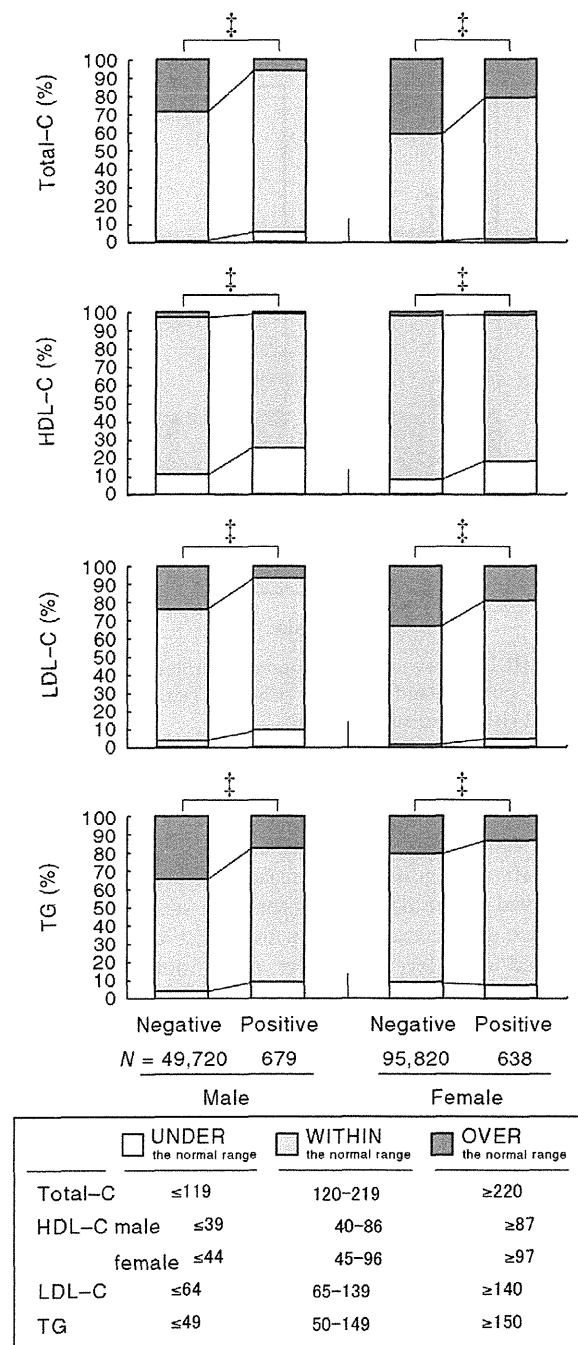
Figure 1 Comparison of the relative ratios of the three classifications of lipids based on the reference values for Japanese clinical examination, between the hepatitis C virus (HCV) negative and positive patients. The respective lipids were divided into under, within and over normal ranges. $\ddagger P < 0.001$ shows a significant difference of the relative ratio between the HCV negative and positive subjects by Pearson's χ^2-test analysis. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Total-C, total cholesterol.

◄

ALT, AST and BMI were carried out to exclude these factors.

Composition of serum lipids between the HCV positive and negative subjects

Figure 2 shows the balance of serum lipid composition by sex between HCV positive and negative subjects. In both sexes, there was no significant differences in the balance of serum lipid composition between HCV positive and negative subjects. Among males, the rates of TG and HDL-C in the HCV positive subjects tended to be lower and higher, respectively, compared with the HCV negative subjects (TG, 42.4 ± 0.1% vs 40.5 ± 0.5%; HDL-C, 18.7 ± 0.03% vs 20.2 ± 0.3%, in the HCV negative vs positive subjects, respectively), but they were not statistically significant. The serum lipid balance in females was almost the same between the HCV negative and positive subjects. The results show that the all serum lipids were reduced equally in subjects with HCV infection.

Serum levels of lipids classified by healthy levels of aminotransferases

The HCV negative and positive subjects were classified into the normal (ALT ≤30 and AST ≤30) and abnormal (ALT >30 and/or AST >30) populations based upon the healthy serum aminotransferase levels. The HCV positive rates were 0.36% and 3.30% in the normal and abnormal populations, respectively. In the HCV negative subjects, 82.1% were in the normal compared with 17.9% that were in the abnormal population (χ^2-test analysis $P < 0.0001$). In contrast, the normal and abnormal populations in the HCV positive were 33.1% and 66.9% ($P < 0.0001$), respectively. Serum lipid levels classified by the aminotransferases are shown in Figure 3. There were significant differences in the lipid levels between the HCV negative and positive subjects in the normal population. In both sexes, all examined lipid levels in the

parameters in all examined lipids. Although this analysis implied that the influence of HCV infection was the strongest risk factor for the lower level of serum lipids, the further analyses by matching sex, age,
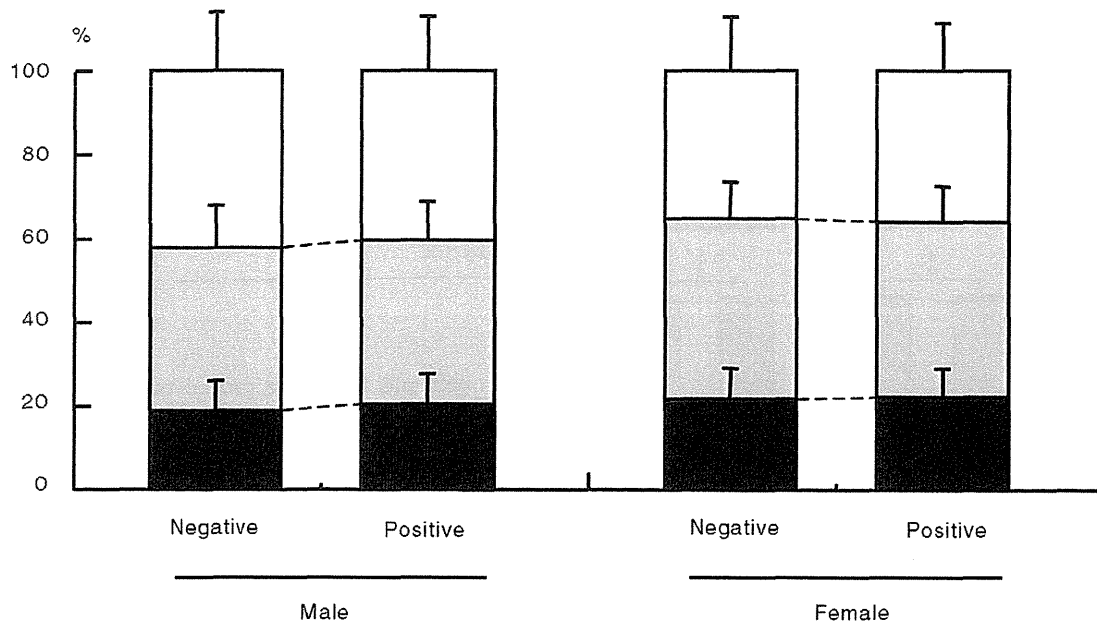
Figure 2 Composition of serum high-density lipoprotein cholesterol (■ HDL-C), low-density lipoprotein cholesterol (☐ LDL-C) and triglyceride (☐ TG) for each sex between the hepatitis C virus positive and negative subjects. Data are shown as mean ± standard deviation of the respective percentage in TG, LDL-C and HDL-C for sum of them.

normal population were significantly lower in the HCV positive compared with the negative subjects, except for TG in females. The significantly lower levels of all examined lipids in the HCV positive were also observed in the abnormal population. The results indicate that the lower levels of serum lipids were associated with the infection of HCV rather than the condition of liver damage.

Differences of lipids among age ranges

Figure 4 shows the differences in the age range of serum lipid levels in 5-year increments in the HCV negative and positive subjects by sex. In both sexes, lower levels of all examined lipids in the HCV positive subjects were observed for all age ranges, except for some younger age ranges for TG level. Among the age ranges under 50 years, the Total-C and LDL-C levels in the HCV negative subjects were lower in females than in males, but the lower levels were reversed in those aged above 50 years. In the HCV positive subjects, however, both levels were weakly influenced by age for both sexes, and therefore the lower levels in males remained unchanged throughout all age ranges.

Serum levels of lipids classified by BMI

Figure 5 shows the serum lipid levels classified by the WHO-defined classification of BMI. In all BMI classes

for both sexes, except for the under Wt class in females, Total-C and LDL-C levels in the HCV positive subjects were significantly lower than in the negative subjects. Similarly, a significant decrease of HDL-C levels was observed in the BMI classes for both sexes in the HCV positive group, except for in the obese class who also showed lower levels; however, this finding was not significant. In TG, lower levels were observed in the HCV positive subjects for all BMI classes in both sexes, and significant differences were found in the normal Wt and over Wt classes for both sexes and for the obese class in males. Accompanied with the higher class of BMI, the typical dyslipidemic patterns of higher TG and lower HDL-C levels were observed in both HCV positive and negative subjects, but the effects of BMI were smaller in HCV positive than in negative subjects.

DISCUSSION

AMONG OVER 140 000 participants undergoing public health examinations, we evaluated the serum lipid profiles in the HCV positive subjects by various host factors including sex, age, nutritional state, hepatic damage and HCV antibody titer. In contrast to HCV hepatitis patients in hospitals, this cohort included
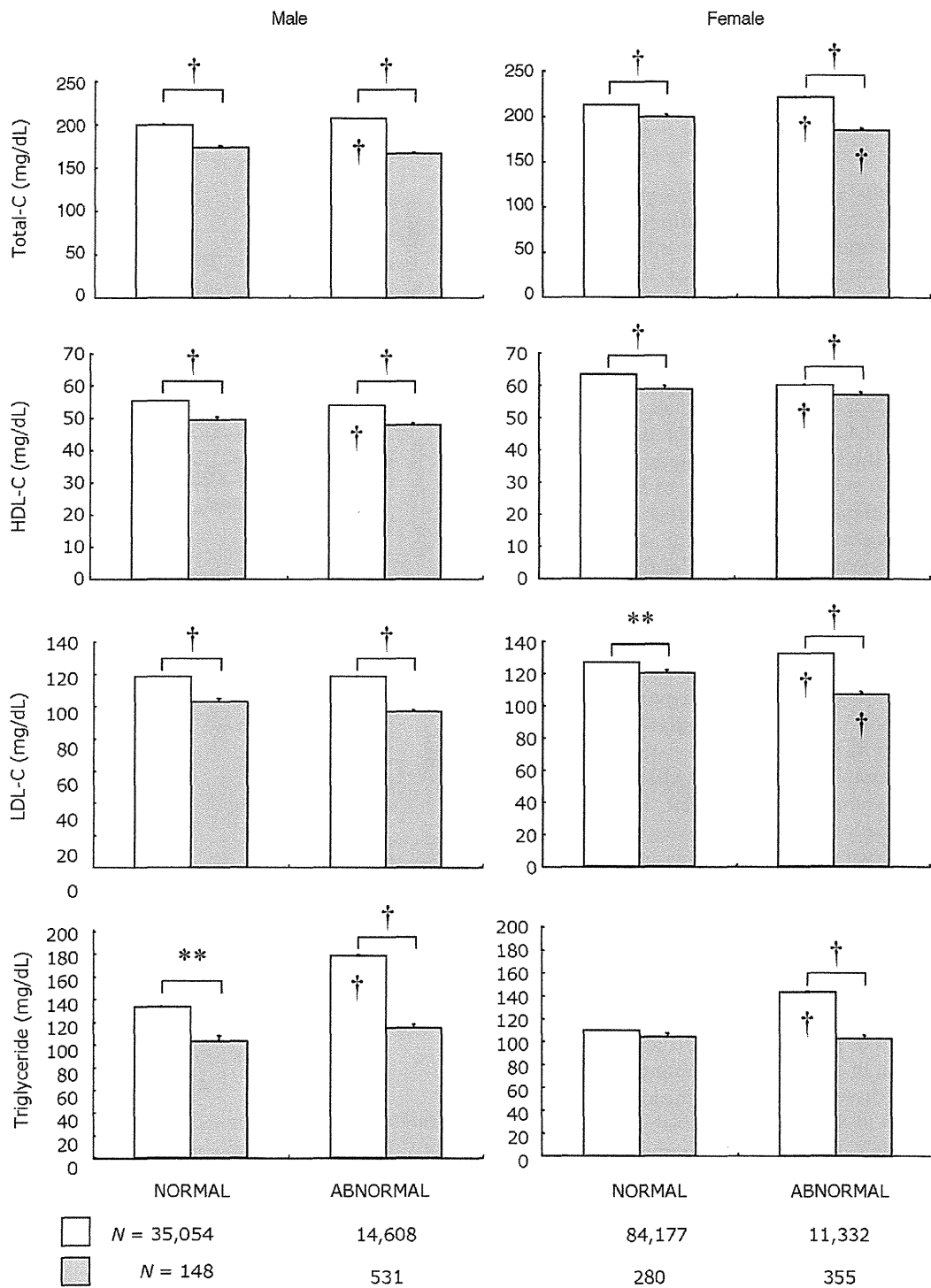
Figure 3 Serum lipid levels classified by the healthy limits of serum aminotransferases in the hepatitis C virus (HCV) (□) negative and (▨) positive subjects. The "normal" and "abnormal" populations were classified by cut-off points: alanine aminotransferase (ALT) ≤30 and aspartate aminotransferase (AST) ≤30, and ALT >30 and/or AST >30, respectively. Data are expressed the mean ± standard error. ANOVA *P*-value was <0.0001 for all lipid parameters in both sexes. **P < 0.01, †P < 0.001 by Bonferroni's post-hoc test. The symbols inside the columns of abnormal without the bar indicate the comparison against the respective normal. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Total-C, total cholesterol.

a significantly large number of asymptomatic HCV positive subjects with normal aminotransferase levels. In general, serum lipid levels are influenced by some factors including sex, age, diseases and/or nutritional states. As shown in Table 2, the multivariate analysis showed that most factors were significantly associated with hypolipidemia, and especially the HCV positive was the strongest factor. In comparison by matching the respective factor, serum levels of all examined lipids (Total-C, HDL-C, LDL-C and TG) were significantly decreased in the HCV positive compared to those in the HCV negative subjects, regardless of sex, age, BMI or serum aminotransferase levels. Furthermore, the significant hypolipidemia was observed in the HCV positive subjects when compared to those of the HCV negative subjects with a prior infection. Particularly, to our knowledge, the hypolipidemia in the HCV positive subjects with normal serum aminotransferase levels have never been reported.

It has been well known that the hypolipidemia caused by impaired liver function is observed in chronic liver diseases including liver cirrhosis.[20,21] Therefore, there is an apprehension whether some cirrhotic patients with lower aminotransferase levels were included in the normal population in the present study or not. In active hepatitis infected with HCV shifting to cirrhosis, both aminotransferase levels tend to decline, but are still above the normal range.[32-34] Accordingly, we assumed that there might be few chronic cirrhotic patients with HCV in the normal population. In addition, the malnutrition is generally found in the chronic cirrhotic patients, and consequently BMI would be lower. However, in the present study, the lower lipid levels were observed in all BMI classes among the HCV positive subjects. These results support the idea that the lipid abnormalities in the HCV positive subjects are directly caused by HCV infection itself rather than by the secondary effects of HCV infection, namely, hepatic damage or nutritional disorder.

Previously, some studies showed that serum LDL-C level was significantly decreased in the patients infected with HCV compared with that in the uninfected subjects.[12,14,17,35] However, serum HDL-C level was unchanged in the HCV positive subjects.[12,14,17,35] In
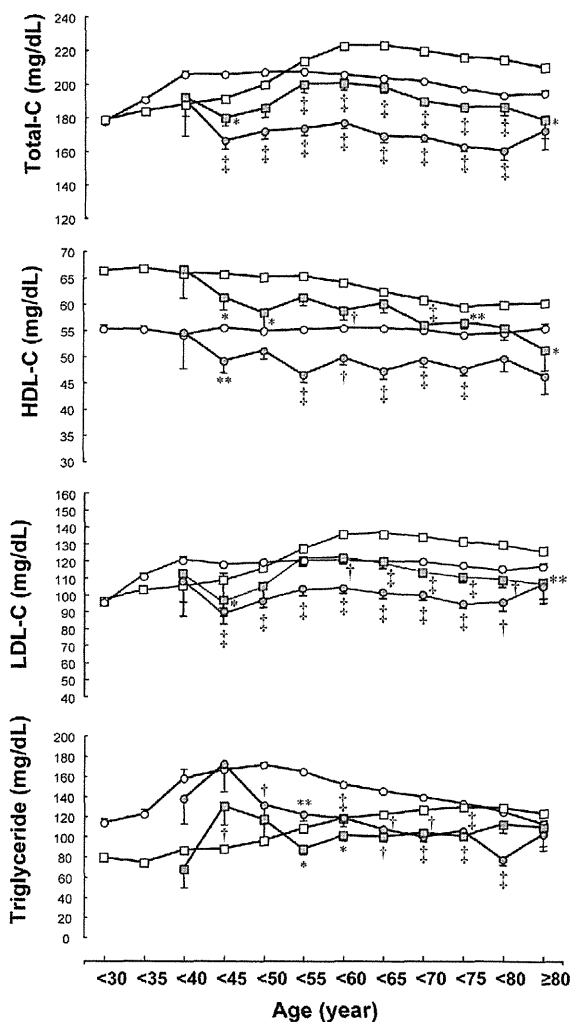

Figure 4 Serum lipid levels stratified by age ranges in the hepatitis C virus (HCV) negative and positive subjects. Data are expressed as the mean ± standard error, and the age ranges were divided into 5-year increments. Significant difference was analyzed by Mann–Whitney *U*-test between the HCV negative and positive subjects in each age-range; *P < 0.05, **P < 0.01, †P < 0.001, ‡P < 0.0001. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Total-C, total cholesterol. (○) HCV-negative: male; (♀) HCV-positive: male; (⬓) HCV-negative: female; (⬓) HCV-positive: female.
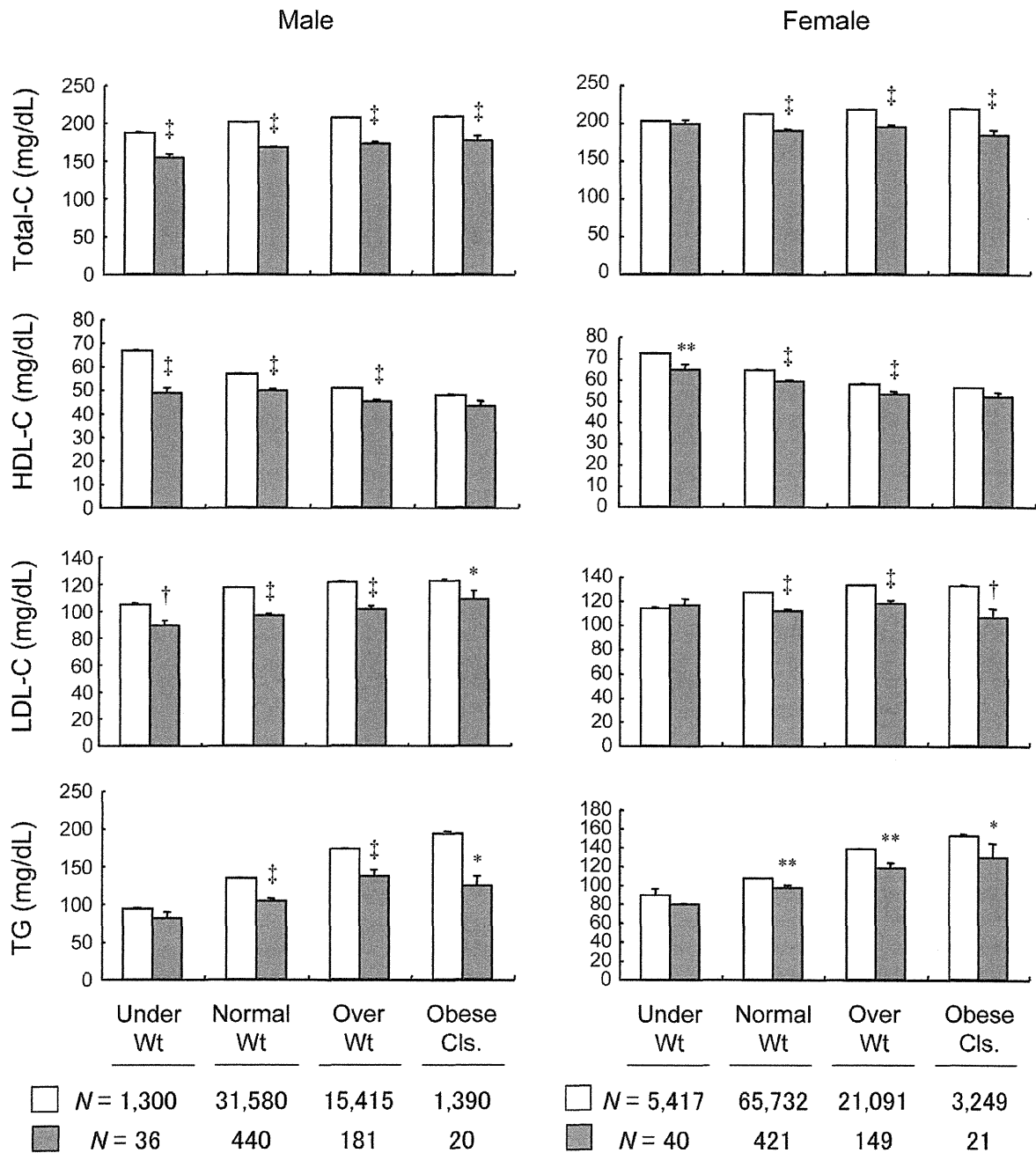
Figure 5 Serum lipid levels classified by the World Health Organization defined body mass index (BMI) class in the hepatitis C virus (HCV) (□) negative and (▨) positive subjects. Data are expressed as the mean ± standard error. Under Wt, underweight (BMI <18.5); Normal Wt, normal range of weight (18.5 ≤ BMI < 25); Over Wt, overweight (25 ≤ BMI < 30); Obese Cls, obese classes 1–3 (BMI ≥30). Significant difference between the HCV negative and positive was analyzed by Mann–Whitney U-test; *P < 0.05, **P < 0.01, †P < 0.001, ‡P < 0.0001. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Total-C, total cholesterol.

contrast, Siagris et al.[15] as well as ourselves, showed that both LDL-C and HDL-C levels were significantly reduced in the HCV positive subjects. The different findings about serum HDL-C level in the HCV positive subjects should be due to the difference in the compared control levels. In the aforementioned studies,[12,17,35] the HDL-C levels of controls were 45–47 mg/dL, which was considerably lower than those in the studies of ourselves and Siagris et al. (53–54 mg/dL).[15] The difference in the HDL-C level in the controls may be due to the population characteristics, including race, dietary culture and lifestyle. Thus, both HDL-C and LDL-C levels would be decreased in the HCV positive subjects who had relatively higher level of HDL-C.

In comparison between presence and absence of HCV infection, different results in serum TG level have been reported. Dai et al. showed the significant decrease of TG level in the HCV positive subjects in a large cohort study.[13] In contrast, there are no significant differences in serum TG level between the HCV infected patients and healthy controls in a relatively younger population (42.0 ± 14.6 years of age).[15] In the present study, we also observed the significant decreases in the TG level, but there was no difference in case of comparison in the relatively younger populations (35–44 years in males, 35–49 years in females, Fig. 4). It is not clear why serum TG level in younger ages would hardly be affected by HCV infection, and further studies are needed.

Furthermore, there are findings that genotypes of HCV are related to the reduction of hepatic lipid metabolisms. In US, Greek, Austrian, African and French patients with HCV genotype 3a, hypocholesterolemia was more remarkable than other genotypes.[14,15,36–38] Furthermore, in Egyptian patients, a significantly lower level of lipids has been also reported in HCV patients predominantly infected with genotype 4.[17] Although the HCV genotype was not determined in the present study because of cohort study in the public health examination, the most common genotypes in the Japanese population are 1b and 2a, while genotypes 3a and 4 are very rare.[39] This genotype population in Japanese is similar to the genotype populations in Taiwan where a lower level of lipids in the HCV carriers has also been reported in a cohort study.[40] Therefore, the abnormalities of serum lipids in the HCV carriers would not depend on the virus genotype.

Several previous studies have reported a relationship between lipid levels and the sustained viral response (SVR) of antivirus therapy in the HCV patients. Corey et al. observed that serum Total-C and LDL-C levels were significantly higher after treatment of peginterferon and ribavirin for approximately 7 months in the HCV patients with SVR compared to those in the non-responder/relapsers whose serum lipid levels did not differ from responder before the initiation of the HCV therapy.[14] Furthermore, Gopal et al. showed that HCV patients with higher LDL-C level before HCV therapy were associated with greater odds of achieving an SVR.[41] Therefore, focusing on the lipid prolife in the HCV patients should have important implications in the antivirus therapy including interferon and ribavirin.

Although the exact reason for the significant decrease of serum lipid levels in the HCV positive subjects is still unclear, previous studies showed HCV impaired assembly and secretion of very low-density lipoprotein from hepatocytes,[42] and reduced transport of lipids by HCV-induced oxidative stress and peroxisome proliferator-activated receptor-α inability.[43,44] In addition, a study of cholesterol metabolism by comprehensive analysis of serum biomarker sterols[45] has suggested that endogenous cholesterol biosynthesis is downregulated while intestinal cholesterol absorption is not reduced in patients with HCV infection.[46] Because lower serum cholesterol concentrations in the HCV patients could not be explained by hepatic damage or malnutrition, HCV itself might downregulate cholesterol biosynthesis in the human body.

In conclusion, the present study demonstrated that the serum levels of lipids including Total-C, LDL-C, HDL-C and TG were significantly lower in the HCV positive subjects than in the negative ones, irrespective of host factors including aminotransferase levels and nutritional states. Therefore, HCV infection itself might directly cause abnormalities of lipid metabolism.

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Special Report

Management of hepatocellular carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009)

Shigeki Arii,[1] Michio Sata,[2] Michiie Sakamoto,[3] Mitsuo Shimada,[4] Takashi Kumada,[5] Shuichiro Shiina,[6] Tatsuya Yamashita,[7] Norihiro Kokudo,[8] Masatoshi Tanaka,[9] Tadatoshi Takayama[10] and Masatoshi Kudo[11]

[1]*Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Medical and Dental University Graduate School of Medicine, [3]Department of Pathology, Keio University School of Medicine, [6]Department of Gastroenterology, University of Tokyo, Graduate School of Medicine, [8]Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, University of Tokyo Graduate School of Medicine, and [10]Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, [2]Department of Gastroenterology and Hepatology, Kurume University School of Medicine, and [9]Department of Gastroenterology, Kurume University Medical Center, Kurume, [4]Department of Surgery, The University of Tokushima, Tokushima, [5]Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, [7]Department of Gastroenterology, Kanazawa University, Graduate School of Medical Science, Kanazawa, [11]Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka-Sayama, Japan*

Hepatocellular carcinoma (HCC) is responsible for approximately 600 000–700 000 deaths worldwide. It is highly prevalent in the Asia–Pacific region and Africa, and is increasing in Western countries. The evidence-based guideline for HCC in Japan was published in 2005 and revised in 2009. Apart from this guideline, a consensus-based practice manual proposed by the HCC expert panel of the Japan Society of Hepatology (JSH), which reflects widely accepted daily practice in Japan, was published in 2007. At the occasion of the 45th Annual meeting of the JSH in Kobe 4–5 June 2009, a consensus meeting of HCC was held. Consensus statements were created based on 67% agreement of 200 expert members. This article describes the up-to-date consensus statements which largely reflect the real world HCC practice in Japan. We believe readers of this article will gain the newest knowledge and deep insight on the management of HCC proposed by consensus of the HCC expert members of JSH.

Key words: hepatocellular carcinoma, Japan Society of Hepatology, staging system, surveillance, treatment algorithm, consensus-based guideline

INTRODUCTION

THE LAST EVIDENCE-BASED guideline for hepatocellular carcinoma (HCC) for Japan was published in 2005,[1] and has prevailed nationwide. This document was developed by a committee composed of 14 experts (Chairman: Professor Masatoshi Makuuchi) and was based on a critical review of 7118 English reports published between 1966 and 2002. This guideline includes

58 research questions regarding important issues for the prevention, diagnosis, surveillance and treatment of HCC. The utility of this guideline is recognized by many Japanese clinicians and has provided a great contribution to clinical practice. However, there are several issues in which solid evidence is still lacking; thus, clear recommendations for clinical practice cannot be stated. In fact, 45% of the research questions are of grade C recommendation level, representing a lack of adequate evidence. These issues are left to the clinician's discretion within the clinical setting. Furthermore, because the guidelines did not include the most up-to-date articles, no recommendation or statements were made regarding newly established evidence. In addition, the clinical practices that follow these guidelines are considered to account for 70–80% of general practice institutions.

As mentioned above, Congress President, Professor Masatoshi Kudo, at the 45th Annual Meeting of the Japan Society of Hepatology organized the Consensus Meeting of Hepatocellular Carcinoma. The program was chaired by Professors M. Sata and S. Arii and covered the updated problems and clarified some controversial issues. Eight experts were selected to contribute to the meeting and they were assigned the following topics based on their specialties. Professor M. Sakamoto presented recommendations regarding diagnostic problems for small-sized HCC from the clinicopathological point of view. Professor M. Shimada discussed the utility of clinical staging and prognosis. Dr T. Kumada reviewed the current status of diagnostic imaging and tumor markers. Dr S. Shiina discussed important issues on ablative treatment. Dr Yamashita reviewed transarterial chemoembolization and chemotherapy. Professor N. Kokudo discussed surgical treatment, including liver transplantation. Dr M. Tanaka presented a treatment algorithm from the point-of-view of hepatologists. Finally, Professor T. Takayama comprehensively discussed the appropriateness of the present treatment algorithm.

In each presentation, the speakers raised clinical questions regarding the remaining problems that needed to be clarified in the present guidelines, and the HCC specialists (a total of 200 physicians: hepatologists, 70%; surgeons, 24%; radiologists, 2%; and pathologists, 4%) answered these questions using a question and answer analyzer system. Recommendations were approved when at least 67% of the HCC experts reached agreement. For instances where agreement was between 50% and 67%, the statements were considered informative, and are cited here as "informative statements".

In this consensus paper, each presenter has provided a summary of the recommendations and consensus. It is highly expected that this Consensus Statement established by the Japan Society of Hepatology (JSH) will provide valuable insight, and will greatly contribute to the future improvement of the guidelines and appropriate clinical practices for patients with HCC worldwide.

PATHOLOGICAL ASSESSMENT

PATHOLOGICAL ASSESSMENT OF HCC is described in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.[2] It focuses on macroscopic typing and tumor grading based on tumor differentiation and reflects the aggressiveness of the tumors; differential diagnosis between multicentric development and intrahepatic metastasis of multiple tumors; and diagnosis of early HCC and precance-

rous lesions. Historically, careful and detailed histological evaluation of surgical specimens enabled us to understand the clinicopathological features of HCC development and extension, and to establish the above-mentioned diagnostic criteria. However, the recent increase in non-surgical treatments for HCC, such as radiofrequency ablation (RFA), is rapidly changing the role and position of pathological diagnosis. Thus, we discussed the indications for liver tumor biopsy for the diagnosis and treatment of HCC.

When we consider the indications for liver biopsy, the risk and benefit of this procedure must be considered.[3–8] The risk includes complications caused by the procedure itself, such as hemorrhage by needle insertion, and by tumor seeding. The incidence of tumor seeding has been reported in approximately 1–5% of cases. Certainly, we have to note that the incidence depends on the characteristics of the tumor such as tumor size and tumor differentiation. Liver biopsy is important in terms of tumor diagnosis, assessment of prognosis and decision making for treatment. For example, for a typical HCC larger than 2 cm in size with a typical vascular pattern on imaging, and elevated tumor markers such as α-fetoprotein (AFP) and/or des-γ-carboxy prothrombin (DCP), the benefit of performing tumor biopsy to confirm the diagnosis of HCC seems minimal. In contrast, only liver biopsy can be used to confirm the diagnosis of cancer in cases with suspected HCC or borderline lesions on clinical and imaging diagnosis. However, controversy remains because of the inconsistent treatment strategy for suspected lesions, particularly in cases with poor liver function.

Previous follow-up data of suspected HCC and borderline lesions showed that the tumors grow slowly during the precancerous or early HCC stages, but grow rapidly in some early HCC cases or in progressed HCC.[9] The transition from slow growing to rapidly growing tumors was supposed to take place once the tumor reaches approximately 1.5 cm in size. Therefore, the proposed recommendations for liver biopsy are as follows.

Recommendation 1. Liver biopsy should be discouraged in cases with a typical HCC over 1.5 cm in size, which shows typical pattern on imaging.

Recommendation 2. Liver biopsy should be considered in cases with a suspected HCC or borderline lesions/early HCC of 1.5 cm in size or less, which does not show typical pattern on imaging.

In addition to these recommendations, the requirement of liver biopsy should increase if the detection and diagnostic ability of imaging techniques increases for